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APPLICATION NUMBER: *60/569,362*
FILING DATE: *May 06, 2004*

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EV 386660417 US

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification	Number of Pages 60	☐ CDs, Number	
☐ Drawing(s)	Number of Sheets	☐ Other (specify)	
☒ Application Data Sheet. See 37 CFR1.76			

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

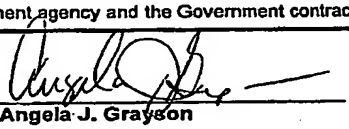
		FILING FEE AMOUNT($)
☐	Applicant claims small entity status. See 37 CFR1.27	
☐	A check or money order is enclosed to cover the filing fees	$160.00
☒	The Director is hereby authorized to charge all required filing fees to, and credit any overpayment to Deposit Account Number: 500329	
☐	Payment by credit card Form PTO-2038 is attached.	

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE 

DATE: May 6, 2004

TYPED or PRINTED NAME Angela J. Grayson

REGISTRATION NO *(if appropriate)* 54,136

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Docket Number. PC32214

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop Provisional Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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PC32214
Provisional Patent Application

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s/ Pamela Hollander
Pamela Hollander, M.A.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:
Hengmaio CHENG

Serial No.: **Not Yet Assigned**

Filed: **Herewith**

For: **NOVEL COMPOUNDS OF PROLINE AND MORPHOLINE DERIVATIVES**

Group Art Unit: **Not Yet Assigned**

Examiner: **Not Yet Assigned**

Honorable Commissioner For Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Transmitted herewith are the following documents:

1. **Return Receipt Postcard**	**1 postcard;**
2. **Application Data Sheet**	**1 page;**
3. **Provisional Patent Application Coversheet**	**1 page (+ duplicate);**
4. **Specification**	**60 Total pages;**
• **Claims**	**10 pages;**
• **Abstract**	**1 page; and**
5. **Fee Due**	**Deposit Account.**

Respectfully submitted,

Date: **May 6, 2004**

Angela J. Grayson
Attorney For Applicants
Registration No. 54,136

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Application Information

Application Type::	**Provisional**
Subject Matter::	**Utility**
Title::	**NOVEL COMPOUNDS OF PROLINE AND MORPHOLINE DERIVATIVES**
Attorney Docket Number::	**PC32214**

Inventor Information

Inventor Authority Type::	**INVENTOR**
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Representative Information

Representative Customer Number::	**28940**

Assignee Information

Assignee Name::	**Agouron Phamaceuticals, Inc.**

NOVEL COMPOUNDS OF PROLINE AND MORPHOLINE DERIVATIVES

Field of Invention

The present invention relates to novel compounds, to pharmaceutical compositions comprising the compounds, as well as to the use of the compounds in medicine and for the preparation of a medicament which acts on the human 11-β-hydroxysteroid dehydrogenase type 1 enzyme (11-β-hsd-1).

Background of the Invention

It has been known for more than half a century that glucocorticoids have a central role in diabetes, e.g. the removal of the pituitary or the adrenal gland from a diabetic animal alleviates the most severe symptoms of diabetes and lowers the concentration of glucose in the blood (Long, C.D. and F.D.W. Leukins (1936) *J. Exp. Med.* 63: 465-490; Houssay, B.A. (1942) *Endocrinology* 30: 884-892). Additionally, it is also well established that glucocorticoids enable the effect of glucagon on the liver.

The role of 11-β-hsd-1 as an important regulator of local glucocorticoid effects and thus of hepatic glucose production is well substantiated (see e.g. Jamieson, et al. (2000) *J. Endocrinol.* 165: p. 685-692). The hepatic insulin sensitivity was improved in healthy human volunteers treated with the non-specific 11-β-hsd-1 inhibitor carbenoxolone (Walker, B.R., et al. (1995) *J. Clin. Endocrinol. Metab.* 80: 3155-3159). Furthermore, the expected mechanism has been established by different experiments with mice and rats. These studies showed that the mRNA levels and activities of two key enzymes in hepatic glucose production were reduced, namely the rate-limiting enzyme in gluconeogenesis, phosphoenolpyruvate carboxykinase (PEPCK), and glucose-6-phosphatase (G6Pase) catalyzing the last common step of gluconeogenesis and glycogenolysis. Finally, the blood glucose level and hepatic glucose production was reduced in mice having the 11-β-hsd-1 gene knocked-out. Data from this model also confirms that inhibition of 11-β-hsd-1 will not cause hypoglycemia, as predicted, since the basal levels of PEPCK and G6Pase are regulated independently of glucocorticoids (Kotelevtsev, Y., et al., (1997) *Proc. Natl. Acad. Sci. USA*, 94: 14924-14929).

Arzneim.-Forsch./Drug Res; 44 (II), No. 7, 821-826, 1994, describes the hypoglycemic compounds 4-(3-methyl-5-oxo-2-pyrazolin-1-yl)benzoic acid and 1-(mesitylen-2-sulfonyl)-1H-1,2,4-triazole. The structures of these compounds differ considerably from the structure of the compounds of the present invention, in that the latter are proline and morpholine derivatives.

Interact with 11-β Compounds that WO 01/90090, WO 01/90091, WO 01/90092, WO 01/90093, WO 03/043999, WO 03/044000, and WO 03/044009 each references compounds that inhibit 11-β-hsd-1. However, the aforementioned publications center on a genus containing a 5-membered heterocyclyl ring.

Endocrine Abstracts, (2003), 5, S23, describes elevated adipose 11-β-hsd-1 underlies the Metabolic Syndrome.

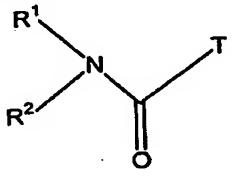
FR 2,384,498 references compounds having a high hypoglycemic effect. Therefore, treatment of hyperglycemia with these compounds may lead to hypoglycemia.

Abdominal obesity is closely associated with glucose intolerance, hyperinsulinemia, hypertriglyceridemia, and other factors of the so-called Metabolic Syndrome (e.g. raised blood pressure, decreased levels of HDL and increased levels of VLDL) (Montague & O'Rahilly, *Diabetes* 49: 883-888, 2000). Obesity is an important factor in Metabolic Syndrome as well as in the majority (>80%) of the type 2 diabetic, and omental fat appears to be of central importance. Inhibition of the enzyme in pre-adipocytes (stromal cells) has been shown to decrease the rate of differentiation into adipocytes. This is predicted to result in diminished expansion (possibly reduction) of the omental fat depot, i.e. reduced central obesity (Bujalska, I.J., Kumar, S., and Stewart, P.M. (1997) *Lancet* 349: 1210-1213).

The compounds of the present invention are 11 β-hsd-1 inhibitors, and are therefore believed to be useful in the treatment of diabetes, obesity, glaucoma, osteoporosis, cognitive disorders, immune disorders, depression, hypertension, and metabolic diseases.

Summary of The Invention

The present invention relates to a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein;

R^1 is $(C_1–C_8)$alkyl, $(CR^4R^5)_k(C_3-C_{12})$cycloalkyl, $(CR^4R^5)_k(C_6-C_{12})$aryl, or $(CR^4R^5)_k$(4-10)-membered heterocyclyl;

k is independently selected from 1 and 2;

j is independently selected from 0, 1, and 2;

t, u, p, q and v are each independently selected from 0, 1, 2, 3, 4, and 5;

T is a (4-10)-membered heterocyclyl containing at least one nitrogen atom and wherein said nitrogen atom is optionally substituted by R^3;

R^2 and R^3 are independently selected from H and $(C_1$–$C_6)$alkyl;

R^4 and R^5 are independently selected from H and $(C_1$-$C_6)$alkyl;

each carbon atom of T, R^1, R^2, and R^3 is optionally substituted by 1 or more R^6 groups;

each R^6 group is selected from the group consisting of halo, cyano, nitro, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, azido, hydroxy, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $-(C=O)-R^7$, $-(C=O)-O-R^7$, $-O-(C=O)-R^7$, $-O-(C=O)-NR^7R^8$, $-NR^8(C=O)-R^9$, $-(C=O)-NR^8R^9$, $-NR^8R^9$, $-NR^8OR^9$, $-S(O)_kNR^8R^9$, $-S(O)_j(C_1$-$C_8)$alkyl, $-O-SO_2-R^9$, $-NR^8-S(O)_k-R^9$, $-(CR^{10}R^{11})_v(C_6$-C_{12} aryl), $-(CR^{10}R^{11})_v(C_3$-$C_{12})$cycloalkyl, $-(CR^{10}R^{11})_v$(4-10)-membered heterocyclyl, $-(CR^{10}R^{11})_q(C=O)(CR^{10}R^{11})_v(C_6$-$C_{12})$aryl, $-(CR^{10}R^{11})_q(C=O)(CR^{10}R^{11})_v$(4-10)-membered heterocyclyl, $-(CR^{10}R^{11})_vO(CR^{10}R^{11})_q(C_6$-$C_{12})$aryl, $-(CR^{10}R^{11})_vO(CR^{10}R^{11})_q$(4-10)-membered heterocyclyl, $-(CR^{10}R^{11})_qS(O)_j(CR^{10}R^{11})_v(C_6$-$C_{12})$aryl, and $-(CR^{10}R^{11})_qS(O)_j(CR^{10}R^{11})_v$(4-10)-membered heterocyclyl;

any 1 or 2 carbon atoms of any (4-10)-membered heterocyclyl moiety of the foregoing R^6 groups are optionally substituted with an oxo group;

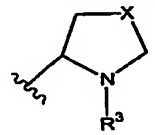
any carbon atom of a $(C_1$-$C_6)$alkyl, a $(C_6$-$C_{12})$aryl and a (4-10)-membered heterocyclyl of the foregoing R^6 groups are optionally substituted with 1 to 3 substituents independently selected from halo, cyano, nitro, $-CF_3$, $-CFH_2$, $-CF_2H$, trifluoromethoxy, azido, $-OR^{12}$, $-(C=O)-R^{12}$, $-(C=O)-O-R^{12}$, $-O-(C=O)-R^{13}$, $-NR^{13}(C=O)-R^{13}$, $-(C=O)-NR^{14}R^{15}$, $-NR^{14}R^{15}$, $-NR^{14}OR^{15}$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $-(CR^{16}R^{17})_u(C_6$-$C_{12})$aryl, and $-(CR^{16}R^{17})_u$(4-10)-membered heterocyclyl;

each R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} group is independently selected from H, $(C_1$-$C_6)$alkyl, $-(C=O)NH(C_1$–$C_6)$alkyl, $-(CR^{18}R^{19})_p(C_6$-$C_{12})$aryl, and $-(CR^{18}R^{19})_p$(4-10)-membered heterocyclyl;

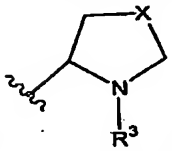
any 1 or 2 carbon atoms of the (4-10)-membered heterocyclyl of said each R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17}group is optionally substituted with an oxo group;

any carbon atoms of a $(C_1$-$C_6)$alkyl, a $(C_6$-$C_{12})$aryl, and a (4-10)-membered heterocyclyl of the foregoing R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} groups are optionally substituted with 1 to 3 substituents independently selected from halo,

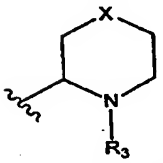
In one embodiment, the invention relates to compounds of formula (I), wherein

T is  and wherein X is O.

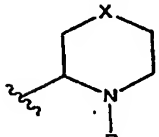
In one embodiment, the invention relates to compounds of formula (I), wherein

T is  and wherein X is $CR^{22}R^{23}$.

In one embodiment, the invention relates to compounds of formula (I), wherein

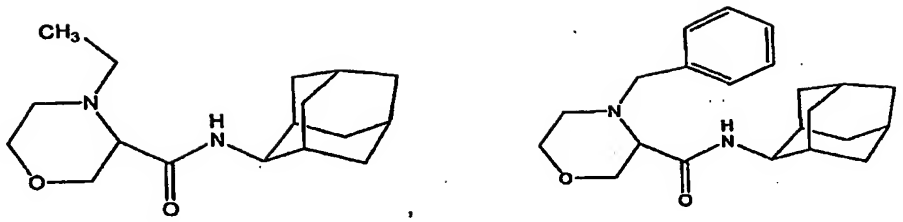
T  and wherein X is O.

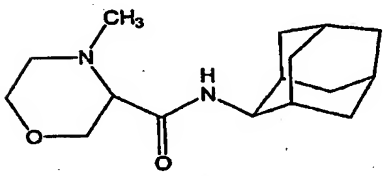
In one embodiment, the invention relates to compounds of formula (I), wherein

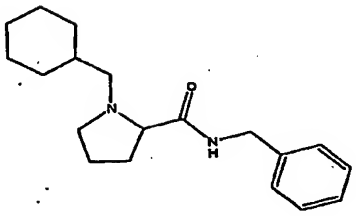
T is  and wherein X is $CR^{22}R^{23}$.

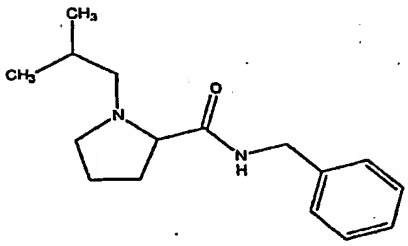
In another embodiment, the invention relates to compounds of formula (I), wherein R^1 is adamantyl, benzyl, phenyl, picolyl, isoindolinyl, pyridinyl, isoquinolyl or cyclohexyl, wherein each carbon atom is optionally substituted by 1 to 10 R^6 groups; wherein each R^6 is independently selected from the group consisting of halo, cyano, CF_3, hydroxy, $(C_1$-$C_6)$alkoxy, $(C_1$–$C_6)$alkyl, and $(C_2$-$C_6)$alkenyl.

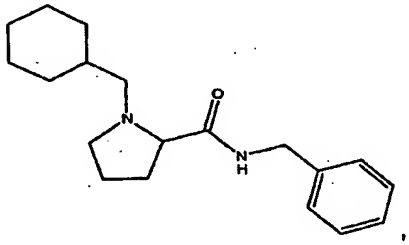
Specific compounds of the present invention are selected from the group consisting of:

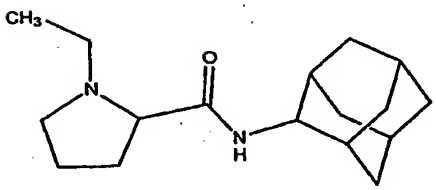


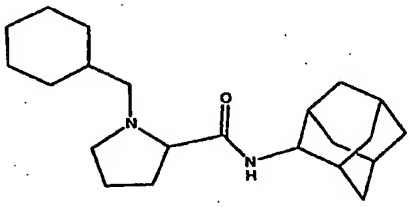


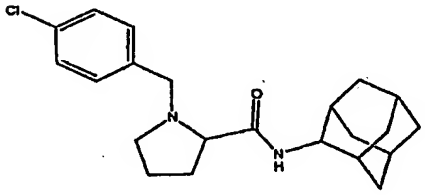


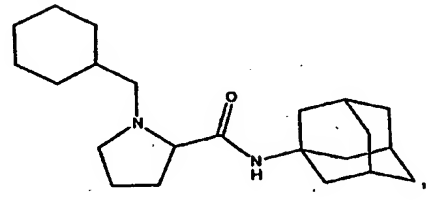












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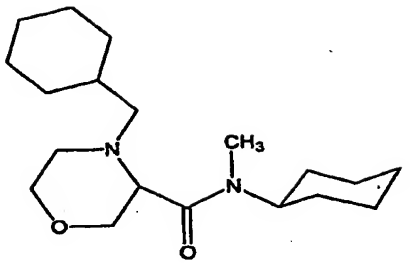
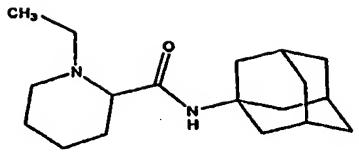
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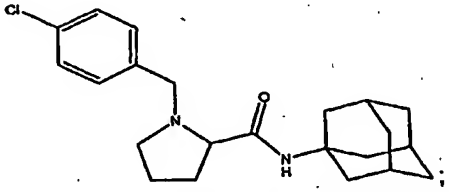
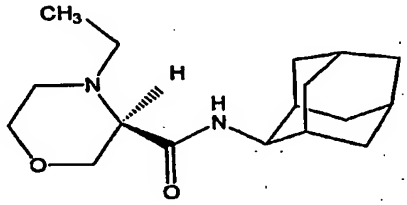
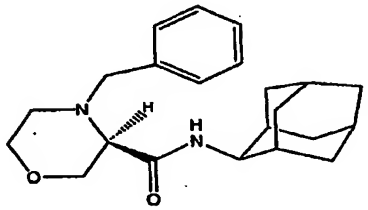
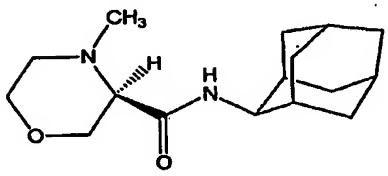
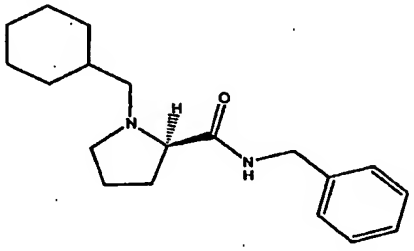
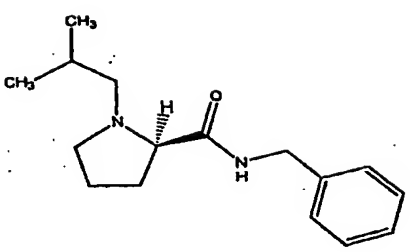
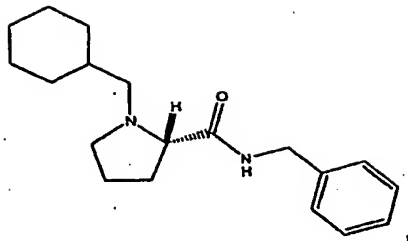


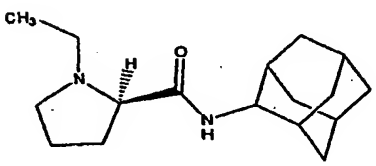
or a pharmaceutically acceptable salt or solvate thereof.

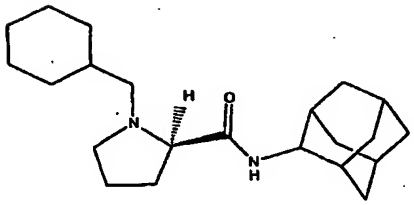
Specific compounds of the present invention are selected from the group consisting of:

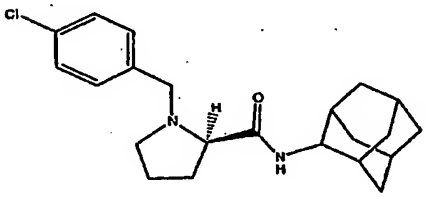





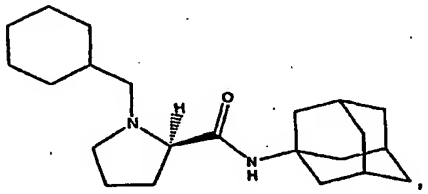


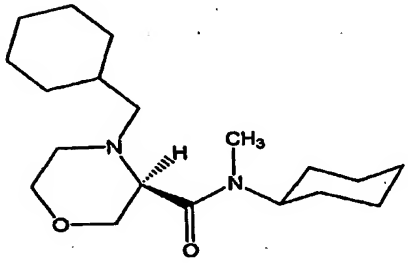


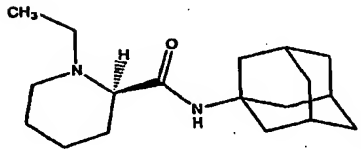




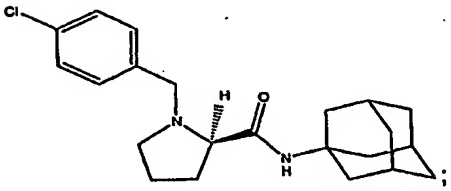








and



;

or a pharmaceutically acceptable salt or solvate thereof.

The present invention also relates to a pharmaceutical composition comprising an effective amount of a compound according to formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating a condition that is mediated by the modulation of the 11-β-hsd-1 enzyme, the method comprising administering to a mammal an effective amount of a compound according to formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The present invention also relates to a method of treating diabetes, metabolic syndrome, insulin resistance syndrome, obesity, glaucoma, hyperlipidemia, hyperglycemia, hyperinsulinemia, osteoporosis, tuberculosis, atherosclerosis, dementia, depression, viral diseases, ophthalmic disorders, inflammatory disorders, or diseases in which the liver is a target organ, the method comprising administering to a mammal an effective amount of a compound according to formula (I) or a pharmaceutically acceptable salt or solvate thereof.

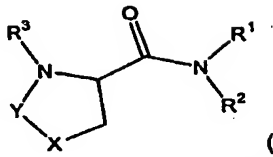
The present invention also relates to a method of treating a condition that is mediated by the modulation of the 11-β-hsd-1 enzyme, the method comprising administering to a mammal an effective amount of a compound according to formula (I), or a pharmaceutically acceptable salt or solvate thereof, with a known therapeutic agent to treat glaucoma.

The present invention also relates to a method of treating a condition comprising administering to a mammal an effective amount of a compound according to formula (I), or a pharmaceutically acceptable salt or solvate thereof, with prostanoid receptor agonist such as latanoprost to treat glaucoma.

The present invention also relates to a method of treating a condition comprising administering to a mammal an effective amount of a compound according to formula (I), or a pharmaceutically acceptable salt or solvate thereof, with a known therapeutic agent such as carbonic anhydrase inhibitor to treat glaucoma.

The present invention also relates to a method of treating a condition comprising administering to a mammal an effective amount of a compound according to formula (I), or a pharmaceutically acceptable salt or solvate thereof, with a known therapeutic agent such as PPAR agonists to treat diabetes.

The present invention also relates to a method of preparing a compound of formula (V)



(V);

wherein R^1 is selected from the group consisting of $(C_1\text{-}C_6)$alkyl; $(CR^4R^5)_t(C_3\text{-}C_{12})$cycloalkyl, $(CR^4R^5)_t(C_6\text{-}C_{12})$aryl, and $(CR^4R^5)_t$(4-10)-membered heterocyclyl;

R^2 is selected from the group consisting of H and $(C_1\text{-}C_6)$alkyl;

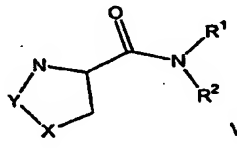
R^3 is selected from the group consisting of $(C_1\text{-}C_6)$alkyl and $NR^{22}R^{23}$;

R^4 and R^5 are independently selected from H and $(C_1\text{-}C_6)$alkyl;

R^{22} and R^{23} are independently selected from H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $-(C=O)\text{-}R^4$, $(CR^4R^5)_t(C_3\text{-}C_{12})$cycloalkyl, $(CR^4R^5)_t(C_6\text{-}C_{12})$aryl, and $(CR^4R^5)_t$(4-10)-membered heterocyclyl;

X is independently selected from the group consisting of $CR^{22}R^{23}$, O, S, and NR^{22};

Y is $(CR^{22}R^{23})_n$ wherein n is independently selected from 1, 2, and 3; comprising:



treating a compound of formula (IV) with R^3-LV in a solvent;

wherein LV is a suitable leaving group and R^3 is defined above.

In one embodiment, the invention relates a method further comprising treating a compound of formula (IV) to form a compound of formula (V) in the presence of a base.

In another embodiment, the invention relates a method further comprising the base selected from the group consisting of K_2CO_3, $NaHCO_3$, and Et_3N.

In yet another embodiment, the invention relates a method further comprising treating a compound of formula (IV) to form a compound of formula (V) at a temperature range from about 20 degrees Celsius to the boiling point of the solvent.

In one embodiment, the invention relates a method further comprising treating a compound of formula (IV) to form a compound of formula (V) by reductive amination in the presence of an aldehyde or ketone in a suitable solvent.

In another embodiment, the invention relates a method further comprising the solvent selected from the group consisting of THF, MeOH, and CH_2Cl_2.

In yet another embodiment, the invention relates a method further comprising treating a compound of formula (IV) to form a compound of formula (V) in the presence of an acid.

In one embodiment, the invention relates a method wherein the acid is acetic acid.

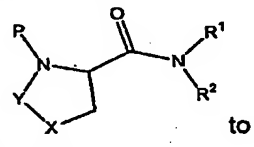
In another embodiment, the invention relates a method further comprising treating a compound of formula (IV) to form a compound of formula (V) in the presence of a reducing agent.

In yet another embodiment, the invention relates a method wherein the reducing agent is selected from the group consisting of $NaBCNH_3$ and $NaB(OAc)_3H$.

In one embodiment, the invention relates a method further comprising treating a compound of formula (IV) to form a compound of formula (V) at a temperature range from about 20 degrees Celsius to 60 degrees Celsius.

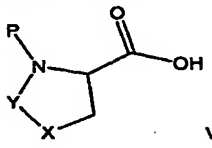
In another embodiment, the invention relates a method further comprising a solvent selected from the group consisting of dichloromethane and N,N-dimethylformamide.

In yet another embodiment, the invention relates a method further comprising the LV selected from the group consisting of halogen and methanesulfonate.

In yet another embodiment, the invention relates a method further comprising treating a compound of formula (III)  to produce a compound of formula (IV) with a suitable deprotecting agent.

In one embodiment, the invention relates a method wherein the deprotecting agent is an acid.

In another embodiment, the invention relates a method wherein the deprotecting agent is trifluoroacetic acid.

In yet another embodiment, the invention relates a method further comprising a method for treating a compound of formula (II)  with an amine to produce a compound of formula (III).

In one embodiment, the invention relates a method wherein the amine is selected from the group consisting of 2-adamantanamine-hydrochloride salt and benzyl amine.

In another embodiment, the invention relates a method further comprising the step of preparing the compound of formula (III) from a compound of formula (II) by treating the compound of formula (II) with at least one activating agent.

In yet another embodiment, the invention relates a method wherein the at least one activating agent is selected from the group consisting of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, 1-hydroxybenzotriazole, and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

Definitions

For purposes of the present invention, as described and claimed herein, the following terms are defined as follows:

As used herein, the terms "comprising" and "including" are used in their open, non-limiting sense.

The term "halo", as used herein, unless otherwise indicated, means fluoro, chloro, bromo or iodo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight or branched moieties.

The term "alkenyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon double bond wherein alkyl is as defined above and including E and Z isomers of said alkenyl moiety.

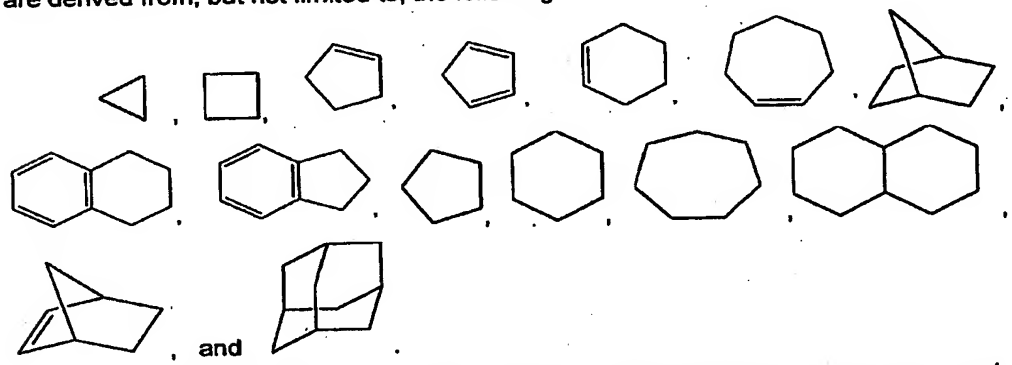
The term "alkynyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon triple bond wherein alkyl is as defined above.

The term "alkoxy", as used herein, unless otherwise indicated, includes O-alkyl groups wherein alkyl is as defined above.

The term "Me" means methyl, "Et" means ethyl, and "Ac" means acetyl.

It is understood that where reference is made to a carbon atom that is "optionally substituted" this refers to a carbon atom bearing at least one hydrogen atom which may be replaced by the stated optional substituent. Further, where a carbon atom is "optionally substituted" with an oxo group, this refers to a carbon atom bearing at least two hydrogen atoms that may be replaced by the oxo group.

The term "cycloalkyl", as used herein, unless otherwise indicated refers to a non-aromatic, saturated or partially saturated, monocyclic or fused, spiro or unfused bicyclic or tricyclic hydrocarbon referred to herein containing a total of from 3 to 10 carbon atoms, preferably 5-8 ring carbon atoms. Exemplary cycloalkyls include monocyclic rings having from 3-10 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and adamantyl. Illustrative examples of cycloalkyl are derived from, but not limited to, the following:

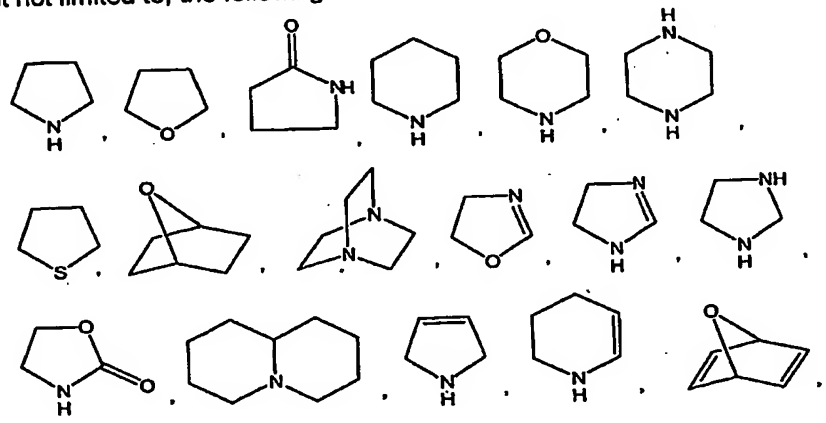


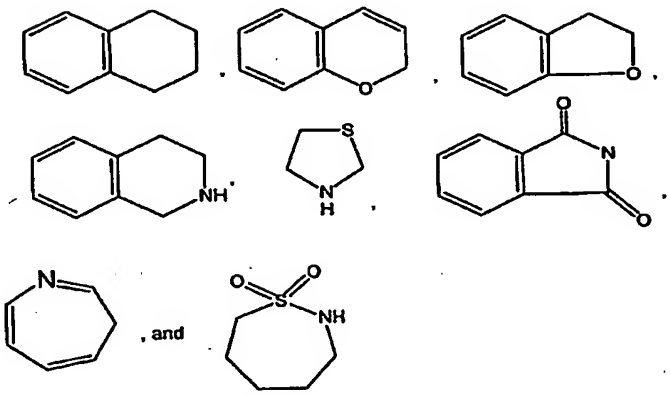
, and

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

The term "(4-10)-membered heterocyclyl", as used herein, unless otherwise indicated, includes aromatic and non-aromatic heterocyclic groups containing one to four heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 4-10 atoms, respectively, in its ring system, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups include groups having only 3 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems. An example of a 3 membered heterocyclic group is aziridine, an example of a 4 membered heterocyclic group is azetidinyl (derived from azetidine). An example of a 5 membered heterocyclic group is thiazolyl, an example of a 7 membered

ring is azepinyl, and an example of a 10 membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups, as derived from the groups listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl (N-attached) or imidazol-2-yl (C-attached). The 4-10 membered heterocyclic may be optionally substituted on any ring carbon, sulfur, or nitrogen atom(s) by one to two oxo, per ring. An example of a heterocyclic group wherein the ring atoms are substituted with oxo moieties is 1,1-dioxo-thiomorpholinyl. Other illustrative examples of 4-10 membered heterocyclic are derived from, but not limited to, the following:





Unless otherwise indicated, the term "oxo" refers to =O.

A "solvate" is intended to mean a pharmaceutically acceptable solvate form of a specified compound that retains the biological effectiveness of such compound. Examples of solvates include compounds of the invention in combination with water, isopropanol, ethanol, methanol, DMSO (dimethylsulfoxide), ethyl acetate, acetic acid, or ethanolamine.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of formula (I). The compounds of formula (I) that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of formula (I) are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edislyate, estolate, esylate, ethylsuccinate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phospate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodode, and valerate salts.

The term "diseases in which the liver is a target organ", as used herein, unless otherwise indicated, means diabetes, hepatitis, liver cancer, liver fibrosis, and malaria.

The term "Metabolic syndrome", as used herein, unless otherwise indicated means psoriasis, diabetes mellitus, wound healing, inflammation, neurodegenerative diseases, galactosemia, maple syrup urine disease, phenylketonuria, hypersarcosinemia, thymine uraciluria, sulfinuria, isovaleric acidemia, saccharopinuria, 4-hydroxybutyric aciduria, glucose-6-phosphate dehydrogenase deficiency, and pyruvate dehydrogenase deficiency.

In the compounds of formula (I), where terms such as $(CR^4R^5)_t$, $(CR^{18}R^{19})_p$, $(CR^{10}R^{11})_v$ or $(CR^{22}R^{23})_n$ are used, R^4, R^5, R^{18}, R^{19}, R^{10}, R^{11} R^{22}, and R^{23} may vary with each iteration of t, v, p or n above 1. For instance, where t, v, p or n is 2 the terms $(CR^4R^5)_t$, $(CR^{18}R^{19})$, $(CR^{10}R^{11})_v$ or $(CR^{22}R^{23})_n$ may equal $-CH_2CH_2-$, or $-CH(CH_3)C(CH_2CH_3)(CH_2CH_2CH_3)-$, or any number of similar moieties falling within the scope of the definitions of R^4, R^5, R^{18}, R^{19}, R^{10} and R^{11}.

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

The term "modulate" or "modulating", as used herein, refers to the ability of a modulator for a member of the steroid/thyroid superfamily to either directly (by binding to the receptor as a ligand) or indirectly (as a precursor for a ligand or an inducer which promotes production of ligand from a precursor) induce expression of gene(s) maintained under hormone expression control, or to repress expression of gene(s) maintained under such control.

The term "obesity" or "obese", as used herein, refers generally to individuals who are at least about 20-30% over the average weight for his/her age, sex and height. Technically, "obese" is defined, for males, as individuals whose body mass index is greater than 27.8 kg/m^2, and for females, as individuals whose body mass index is greater than 27.3 kg/m^2. Those of skill in the art readily recognize that the invention method is not limited to those who fall within the above criteria. Indeed, the method of the invention can also be advantageously practiced by individuals who fall outside of these traditional criteria, for example, by those who may be prone to obesity.

The term "inflammatory disorders", as used herein, refers to disorders such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, chondrocalcinosis, gout, inflammatory bowel disease, ulcerative colitis, Crohn's disease, fibromyalgia, and cachexia.

The phrase "therapeutically effective amount", as used herein, refers to that amount of drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other.

The phrase "amount . . . effective to lower blood glucose levels", as used herein, refers to levels of compound sufficient to provide circulating concentrations high enough to accomplish the desired effect. Such a concentration typically falls in the range of about 10 nM up to 2 μM; with concentrations in the range of about 100 nM up to 500 nM being one example. As noted previously, since the activity of different compounds which fall within the definition of formula (I) as set forth above may vary considerably, and since individual subjects may present a wide variation in severity of symptoms, it is up to the practitioner to determine a subject's response to treatment and vary the dosages accordingly.

The phrase "insulin resistance", as used herein, refers to the reduced sensitivity to the actions of insulin in the whole body or individual tissues, such as skeletal muscle tissue, myocardial tissue, fat tissue or liver tissue. Insulin resistance occurs in many individuals with or without diabetes mellitus.

The phrase "insulin resistance syndrome", as used herein, refers to the cluster of manifestations that include insulin resistance, hyperinsulinemia, non insulin dependent diabetes mellitus (NIDDM), arterial hypertension, central (visceral) obesity, and dyslipidemia.

Certain compounds of formula (I) may have asymmetric centers and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds of formula (I), and mixtures thereof, are considered to be within the scope of the invention. With respect to the compounds of formula (I), the invention includes the use of a racemate, one or more enantiomeric forms, one or more diastereomeric forms, or mixtures thereof. The compounds of formula (I) may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

Certain functional groups contained within the compounds of the present invention can be substituted for bioisosteric groups, that is, groups which have similar spatial or electronic requirements to the parent group, but exhibit differing or improved physicochemical or other properties. Suitable examples are well known to those of skill in the art, and include, but are not limited to moieties described in Patini et al., Chem. Rev, 1996, 96, 3147-3176 and references cited therein.

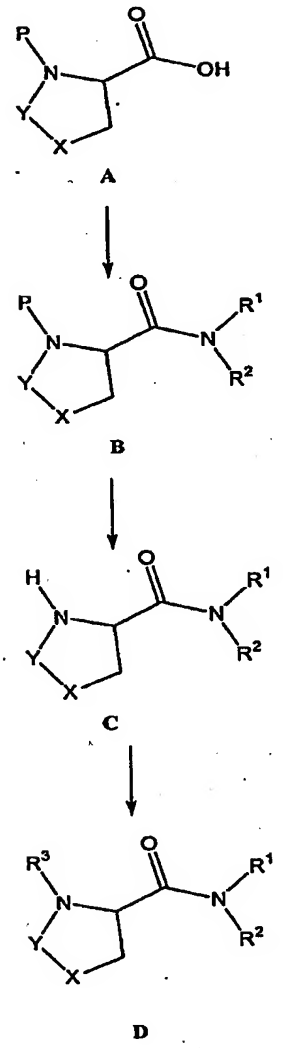
The subject invention also includes isotopically-labelled compounds, which are identical to those recited in formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds of the present invention and pharmaceutically acceptable salts or solvates of said compounds which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be more useful in some circumstances. Isotopically labeled compounds of formula (I) of this invention thereof can generally be prepared by carrying out the procedures found in the Schemes and/or in the Examples below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

Other aspects, advantages, and features of the invention will become apparent from the detailed description below.

Detailed Description And Embodiments of The Invention

The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated, $R^{1} - R^{23}$, and T in the reaction schemes and the discussion that follows are as defined above.

Scheme 1



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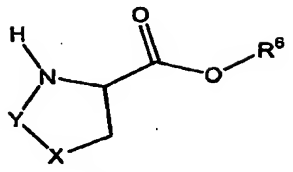
Scheme 2



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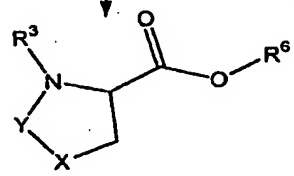

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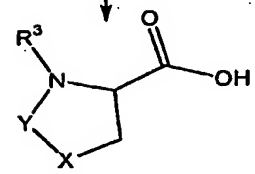

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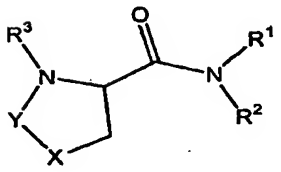

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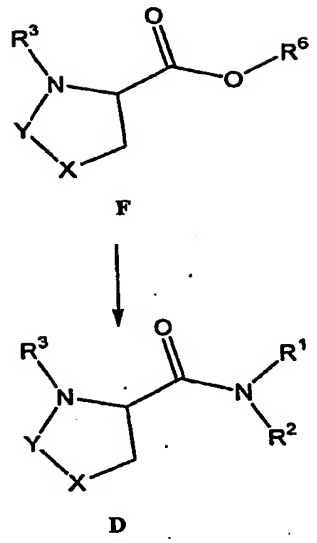
Scheme 3



F

D

Referring to Scheme 1 above, the compound of formula **D** may be prepared by reacting a compound of formula **C** with R^3Q wherein Q is a suitable leaving group such as Cl, Br, I, OMs, etc. in a suitable solvent (e.g. dichloromethane or DMF) advantageously, in the presence of a suitable base (e.g. K_2CO_3, $NaHCO_3$, Et_3N), from room temperature to the boiling point of the solvent, typically from about 20 degrees Celsius to about 100 degrees Celsius. Alternatively, the compound of formula **D** can also be prepared by reductive amination of compound of formula **C** with a suitable aldehyde or ketone in a suitable solvent such as THF, MeOH, CH_2Cl_2, in the presence of a suitable acid such as acetic acid, and a suitable reducing agent such as $NaBCNH_3$ or $NaB(OAc)_3H$ at a temperature ranging from room temperature to 60 degrees Celsius. Compound of formula **C** can be prepared by removing the protecting group P in the compound of formula **B** by treating the compound of formula **B** with a suitable acid. The compound of formula **B** can be prepared by coupling the compound of formula **A** with a suitable amine, such as R^1R^2NH following any suitable amide bond formation methods known to those skilled in the art. Compound formula **A** is an acid and P is a protecting functional group such as BOC or CBZ; R^1 is independently alkyl, cycloalkyl, aryl, or (4-10)-membered heterocyclyl, etc., and R^2 is independently H and

alkyl; X is independently $CR^{22}R^{23}$, O, S, NR^2, etc; and Y is $(CR^{22}R^{23})_n$ wherein n is 1, 2, or 3.

Referring to Scheme 2 above, the compound of formula D can be prepared by coupling the compound of formula G with R^1R^2NH following any suitable amide bond formation methods known to those skilled in the art. Compound of formula G may be prepared by treatment of compound of formula F with a suitable base such as NaOH, KOH, LiOH in a suitable solvent such as MeOH and water at a temperature ranging from room temperature to 60 degrees Celsius. Compound of formula F may be prepared by reacting a compound of formula E with R^3Q wherein Q is a suitable leaving group such as Cl, Br, I, OMs, etc., in a suitable solvent (e.g. dichloromethane or DMF) advantageously, in the presence of a suitable base (e.g. K_2CO_3, $NaHCO_3$, Et_3N), from room temperature to the boiling point of the solvent, typically from about 20 degrees Celsius to about 100 degrees Celsius. Alternatively, the compound of formula F can also be prepared by reductive amination of compound of formula E with an suitable aldehyde or ketone in a suitable solvent such as THF, MeOH, CH_2Cl_2, in the presence of a suitable acid such as acetic acid, and a suitable reducing agent such as $NaBCNH_3$ or $NaB(OAc)_3H$ at a temperature ranging from room temperature to 60 degrees Celsius. Compound E is an amine wherein R^6 is a suitable protecting functional group such as Me; R^1 is independently alkyl, cycloalkyl, aryl, or (4-10)-membered heterocyclyl, etc and R^2 is independently H and alkyl; X is independently $CR^{22}R^{23}$, O, S, NR^2, etc.; and Y is $(CR^{22}R^{23})_n$ wherein n is 1, 2, or 3.

Referring to Scheme 3 above, the compound of formula D can be prepared by treatment of the compound of formula F with R^1R^2NH in a suitable solvent at a suitable temperature or in a suitable solvent in the presence of a suitable acid, such as $AlCl_3$.

The compounds of the present invention may have asymmetric carbon atoms, and may therefore be made from starting materials that are sterospecific. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixtures into a diastereomric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. All such isomers, including diastereomeric mixtures and pure enantiomers are considered as part of the invention.

The compounds of formula (I) that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of formula (I) from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The desired acid salt can also be precipitated from a solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid.

Those compounds of formula (I) that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of formula (I). Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium, and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

The compounds of the present invention may be modulators of 11-β-hsd-1. The compounds of the present invention may modulate processes mediated by 11-β-hsd-1, which refer to biological, physiological, endocrinological, and other bodily processes which are mediated by receptor or receptor combinations which are responsive to the 11-β-hsd-1 inhibitors described herein (e.g., diabetes, hyperlipidemia, obesity,

impaired glucose tolerance, hypertension, fatty liver, diabetic complications (e.g. retinopathy, nephropathy, neurosis, cataracts and coronary artery diseases and the like), arteriosclerosis, pregnancy diabetes, polycystic ovary syndrome, cardiovascular diseases (e.g. ischemic heart disease and the like), cell injury (e.g.) brain injury induced by strokes and the like) induced by atherosclerosis or ischemic heart disease, gout, inflammatory diseases (e.g. arthrosteitis, pain, pyrexia, rheumatoid arthritis, inflammatory enteritis, acne, sunburn, psoriasis, eczema, allergosis, asthma, GI ulcer, cachexia, autoimmune diseases, pancreatitis and the like), cancer, osteoporosis and cataracts. Modulation of such processes can be accomplished in vitro or in vivo. In vivo modulation can be carried out in a wide range of subjects, such as, for example, humans, rodents, sheep, pigs, cows, and the like.

The compounds according to the present invention may be used in several indications which involve modulations of 11-β-hsd-1 enzyme. Thus, the compounds according to the present invention may be used against dementia (see WO97/07789), osteoporosis (see Canalis E 1996, Mechanisms of glucocorticoid action in bone: implications to glucocorticoid-induced osteoporosis, Journal of Clinical Endocrinology and Metabolism, 81, 3441-3447) and may also be used disorders in the immune system (see Franchimont et al, "Inhibition of Th1 immune response by glucocorticoids: dexamethasone selectively inhibits IL-12-induced Stat 4 phosphorylation in T lymphocytes", The Journal of Immunology 2000, Feb 15, vol 164 (4), pages 1768-74) and also in the above listed indications.

Inhibition of 11-β-hsd-1 in mature adipocytes is expected to attenuate secretion of the plasminogen activator inhibitor 1 (PAI-1) an independent cardiovascular risk factor (Halleux, C. M. et al. (1999) J. Clin. Endocrinol. Metab. 84: 4097-4105). Furthermore, there is a clear correlation between glucocorticoid "activity" and cardiovascular risk factor suggesting that a reduction of the glucocorticoid effects would be beneficial (Walker, B.R., et al., (1998), *Hypertension* 31: 891-895; Fraser, R., et al., (1999), *Hypertension*, 33: 1364-1368).

Adrenalectomy attenuates the effect of fasting to increase both food intake and hypothalamic neuropeptide Y expression. This supports the role of glucocorticoids in promoting food intake and suggests that inhibition of 11-β-hsd-1 in the brain might increase satiety and therefore reduce food intake (Woods, S.C., et al., (1998), *Science*, 280:1378-1383).

Possible Beneficial Effect on the Pancreas

Inhibition of 11-β-hsd-1 in isolated murine pancreatic β-cells improves the glucose-stimulated insulin secretion (Davani, B., et al. (2000) *J. Biol. Chem.*, Nov. 10, 2000; 275(45): 34841-4). Glucocorticoids were previously known to reduce pancreatic insulin release in vivo (Billaudel, B. and B.C.J. Sutter, (1979), *Horm. Metab. Res.* 11: 555-560). Thus, inhibition of 11-β-hsd-1 is predicted to yield other beneficial effects for diabetes treatment, besides effects on liver and fat.

Stress and glucocorticoids influence cognitive function (de Quervain, D.J.-F., B. Roozendaal, and J.L. McGaugh, (1998), *Nature*, 394: 787-790). The enzyme 11-β-hsd-1 controls the level of glucocorticoid action in the brain and thus contributes to neurotoxicity (Rajan, V., Edwards, C.R.W. and Seckl, J.R., (1996) *Neuroscience* 16: 65-70; Seckl, J.R., *Front. Neuroendocrinol.*, (2000), 18: 49-99). Unpublished results indicate significant memory improvement in rats treated with a non-specific 11-β-hsd-1 inhibitor. Based the above and on the known effects of glucocorticoids in the brain, it may also be suggested that inhibiting 11-β-hsd-1 in the brain may result in reduced anxiety (Tronche, F., et al., (1999), *Nature Genetics* 23: 99-103). Thus, taken together, the hypothesis is that inhibition of 11-β-hsd-1 in the human brain would prevent reactivation of cortisone into cortisol and protect against deleterious glucocorticoid-mediated effects on neuronal survival and other aspects of neuronal function, including cognitive impairment, depression, and increased appetite (previous section).

The general perception is that glucocorticoids suppress the immune system. But in fact there is a dynamic interaction between the immune system and the HPA (hypothalamo-pituitary-adrenal) axis (Rook, G. A.W., (1999), *Baillier's Clin. Endocrinol. Metab.*, 13: 576-581). The balance between the cell-mediated response and humoral responses is modulated by glucocorticoids. A high glucocorticoid activity, such as at a state of stress, is associated with a humoral response. Thus, inhibition of the enzyme 11-β-hsd-1 has been suggested as a means of shifting the response towards a cell-based reaction.

In certain disease states, including tuberculosis, lepra and psoriasis the immune reaction is normaly biased towards a humoral response when in fact the appropriate response would be cell based. Temporal inhibition of 11-β-hsd-1, local or systemic, might be used to push the immune system into the appropriate response (Mason, D., (1991), *Immunology Today* , 12: 57-60; Rook, et al., *supra*).

Recent data suggests that the levels of the glucocorticoid target receptors and the 11-β-hsd-1 enzymes determine the susceptibility to glaucoma (Stokes, J., et al.,

(2000) *Invest. Ophthalmol.*, 41:1629-1638). Further, inhibition of 11-β-hsd-1 was recently presented as a novel approach to lower the intraocular pressure (Walker , E. A., et al, poster P3-698 at the Endocrine society meeting June 12-15, 1999, San Diego). Ingestion of carbenoxolone, a non-specific inhibitor of 11-β-hsd-1, was shown to reduce the intraocular pressure by 20% in normal subjects. In the eye, expression of 11-β-hsd-1 is confined to basal cells of the corneal epithelium and the non-pigmented epithelialium of the cornea (the site of aqueous production), to ciliary muscle and to the sphincter and dilator muscles of the iris. In contrast, the distant isoenzyme 11 beta-hydroxysteroid dehydrogenase type 2 is highly expressed in the non-pigmented ciliary epithelium and corneal endothelium. None of the enzymes is found at the trabecular meshwork, the site of drainage. Thus, 11-β-hsd-1 is suggested to have a role in aqueous production, rather than drainage, but it is presently unknown if this is by interfering with activation of the glucocorticoid or the mineralocorticoid receptor, or both.

Glucocorticoids have an essential role in skeletal development and function but are detrimental in excess. Glucocorticoid-induced bone loss is derived, at least in part, via inhibition of bone formation, which includes suppression of osteoblast proliferation and collagen synthesis (Kim, C.H., Cheng, S.L., and Kim, G.S., (1999) *J. Endocrinol.*, 162: 371-379). The negative effect on bone nodule formation could be blocked by the non-specific inhibitor carbenoxolone suggesting an important role of 11-β-hsd-1 in the glucocorticoid effect (Bellows, C.G., Ciaccia, A. and. Heersche, J.N.M, (1998), *Bone* 23: 119-125). Other data suggest a role of 11-β-hsd-1 in providing sufficiently high levels of active glucocorticoid in osteoclasts, and thus in augmenting bone resorption (Cooper, M.S., et al., (2000), *Bone*, 27:375-381). Taken together, these different data suggest that inhibition of 11-β-hsd-1 may have beneficial effects against osteoporosis by more than one mechanism working in parallel.

Bile acids inhibit 11β-hydroxysteroid dehydrogenase type 2. This results in a shift in the overall body balance in favor of cortisol over cortisone, as shown by studying the ratio of the urinary metabolites (Quattropani, C., Vogt, B., Odermatt, A., Dick, B. Frey, B.M., Frey, F.J., Nov. 2001, *J Clin Invest.*, 108(9):1299-305. "Reduced activity of 11beta-hydroxysteroid dehydrogenase in patients with cholestasis"). Reducing the activity of 11-β-hsd-1 in the liver by a selective inhibitor is predicted to reverse this imbalance, and acutely counter the symptoms such as hypertension, while awaiting surgical treatment removing the biliary obstruction.

By the expression "comprising" means "including but not limited to." Thus, other non-mentioned substances, additives or carriers may be present.

The compounds of the present invention may also be useful in the treatment of other metabolic disorders associated with impaired glucose utilization and insulin resistance include major late-stage complications of NIDDM, such as diabetic angiopathy, atherosclerosis, diabetic nephropathy, diabetic neuropathy, and diabetic ocular complications such as retinopathy, cataract formation and glaucoma, and many other conditions linked to NIDDM, including dyslipidemia glucocorticoid induced insulin resistance, dyslipidemia, polycysitic ovarian syndrome, obesity, hyperglycemia, hyperlipidemia, hypercholesteremia, hypertriglyceridemia, hyperinsulinemia, and hypertension. Brief definitions of these conditions are available in any medical dictionary, for instance, Stedman's Medical Dictionary (10^{th} Ed.).

Assay

The inhibition constant, Ki, was measured in a buffer containing 100 mM triethanolamine, 200 mM NaCl, 0.02% n-dodecyl β-maltoside, 5% glycerol, 5 mM β-mercaptoethanol, 1% DMSO, pH 8.0. In a typical assay, the activity of human 11b-hsd-1 is measured on a Corning 96-well plate for a total volume of 300 uL/well in the presence and absence of inhibitor. In each well, varying amounts of compounds are incubated with a fixed amount of 11b-hsd-1 (4 nM) and NADPH (500 uM) for 30 to 40 min at room temperature in the assay buffer. The enzyme concentration was determined by titration using reversible tight-binding inhibitors. The activity remaining after the pre-incubation period is measured by adding a fixed concentration of 3H-cortisone (200 nM) and the regeneration system constituted with 2 mM glucose-6-phosphate, 1 U/mL glucose-6-phosphate dehydrogenase and 6 mM $MgCl_2$. The final concentration of cortisone in the assay buffer is lower than the K_m value (328 nM). In each well, the enzyme activity is quenched by mixing an aliquot of the assay buffer with an equal volume of DMSO in a second 96-well plate. 15 uL of these final samples are loaded on a C-18A column, Varian Polaris (3 um, 50 x 4.6 mm) connected to an Agilent 1100 HPLC with 96-well plate autosampler and a β-ram detector from IN/US System. 3H-Cortisone and 3H-cortisol are separated on the column using an isocratic mixture of 38%-62% methanol-water. The area of 3H-cortisol is calculated and plotted versus time to determine a linear velocity. A K_i value was then determined using the following equation from J.F. Morrison (1969):

$$\frac{v_i}{v_o} = 1 - \left(\frac{(I + E + K_i) - \sqrt{(I + E + K_i)^2 - 4.I.E}}{2.I}\right)$$

Where v_i, and v_o are the rates of cortisol formation in the presence and in the absence of inhibitor, respectively, I is the inhibitor concentration and E is the 11b-hsd-1 concentration in the assay buffer. All the concentrations reported are the final concentrations in the assay buffer

See also Morrison, J.F., "Kinetics of the reversible inhibition of enzyme-catalysed reactions by tight-binding inhibitors," *Biochim Biophys Acta.*, 1969; 185: 269-86.

[1,2-3H]-cortisone was purchased from American Radiolabeled Chemicals Inc. NADPH, Glucose-6-Phosphate (G6P), and Glucose-6-Phosphate dehydrogenase were purchased from Sigma.

Pharmaceutical Compositions/Formulations, Dosaging and Modes of Administration

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. In addition, those of ordinary skill in the art are familiar with formulation and administration techniques. Such topics would be discussed, *e.g.* in Goodman and Gilman's The Pharmaceutical Basis of Therapeutics, current edition, Pergamon Press; and Remington's Pharmaceutical Sciences, current edition, Mack Publishing, Co., Easton, Pa. These techniques can be employed in appropriate aspects and embodiments of the methods and compositions described herein. The following examples are provided for illustrative purposes only and are not meant to serve as limitations of the present invention.

The compounds of formula (I) may be provided in suitable topical, oral and parenteral pharmaceutical formulations for use in the treatment of 11-β-hsd-1 mediated diseases. The compounds of the present invention may be administered orally as tablets or capsules, as oily or aqueous suspensions, lozenges, troches, powders, granules, emulsions, syrups or elixirs. The compositions for oral use may include one or more agents for flavoring, sweetening, coloring and preserving in order to produce pharmaceutically elegant and palatable preparations. Tablets may contain pharmaceutically acceptable excipients as an aid in the manufacture of such tablets. As is conventional in the art these tablets may be coated with a pharmaceutically acceptable enteric coating, such as glyceryl monostearate or glyceryl distearate, to

delay disintegration and absorption in the gastrointestinal tract to provide a sustained action over a longer period.

Formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions normally contain active ingredients in admixture with excipients suitable for the manufacture of an aqueous suspension. Such excipients may be a suspending agent, such as sodium carboxymethyl cellulose, methyl cellulose, hydroxypropylmethyl cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; a dispersing or wetting agent that may be a naturally occurring phosphatide such as lecithin, a condensation product of ethylene oxide and a long chain fatty acid, for example polyoxyethylene stearate, a condensation product of ethylene oxide and a long chain aliphatic alcohol such as heptadecaethylenoxycetanol, a condensation product of ethylene oxide and a partial ester derived from a fatty acid and hexitol such as polyoxyethylene sorbitol monooleate or a fatty acid hexitol anhydrides such as polyoxyethylene sorbitan monooleate.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to known methods using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be formulated as a suspension in a non toxic perenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringers solution and isotonic sodium chloride solution. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at about 25 Celcius but liquid at rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and other glycerides.

For topical use preparations, for example, creams, ointments, jellies solutions, or suspensions, containing the compounds of the present invention are employed.

The compounds of formula (I) may also be administered in the form of liposome delivery systems such as small unilamellar vesicles, large unilamellar vesicles and multimellar vesicles. Liposomes can be formed from a variety of phospholipides, such as cholesterol, stearylamine or phosphatidylcholines.

Dosage levels of the compounds of the present invention are of the order of about 0.5 mg/kg body weight to about 100 mg/kg body weight. An exemplary dosage rate is between about 30 mg/kg body weight to about 100 mg/kg body weight. It will be understood, however, that the specific dose level for any particular patient will depend upon a number of factors including the activity of the particular compound being administered, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy. To enhance the therapeutic activity of the present compounds they may be administered concomitantly with other orally active antidiabetic compounds such as the sulfonylureas, for example, tolbutamide and the like.

The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations. In the following examples molecules with a single chiral center, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted, exist as a racemic mixture of diastereomers. Single enantiomers/diastereomers may be obtained by methods known to those skilled in the art.

Where HPLC chromatography is referred to in the preparations and examples below, the general conditions used, unless otherwise indicated, are as follows. The column used is an Alltech Platinum EPS 100A 1.5 micron C18 column; 33mm × 7mm. The samples are run on a Hewlett Packard- 1100 system. A gradient solvent method is used running 5% acetonitrile in water (0.1% trifluoroacetic acid) to 95% acetonitrile in water (0.1% trifluoroacetic acid) over 5.5 minutes. The system then proceeds on a wash cycle with 95 percent acetonitrile in water (0.1% trifluoroacetic acid) for 1.5 minutes. The flow rate over this period is a constant 1.5 mL / minute.

In the following examples and preparations, "Et" means ethyl, "AC" means acetyl, "Me" means methyl, "ETOAC" or "ETOAc" means ethyl acetate, "THF" means tetrahydrofuran, and "Bu" means butyl, "DMSO" means dimethylsulfoxide, "Boc" means

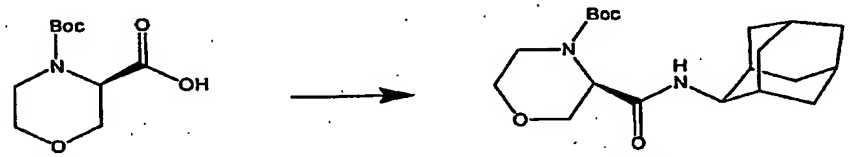
t-butoxycarbonyl, "CBZ" means benzyloxycarbonyl , "OMs " means methanesulfonate, "HATU" means O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, "DMF" means N,N-dimethylformamide, "TFA" means trifluoroacetic acid, "TEA" means triethylamine, "DMAP" means 4-(dimethylamino)pyridine, "EDC" means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, "HOBt" 1-hydroxybenzotriazole, "NMM" means N-methyl-morpholine, "MTBE" means tert-butyl methyl ether.

Also, in Table 1, the term "min" refers to minutes, the term "MS" refers to mass spectroscopy, the term *m/z* refers the mass/charge ratio, the term "HPLC" refers to high performance liquid chromatography, the term "% inhibition at 0.1 nM" refers to activity against 11-β-hsd-1 enzyme as measured by the assay as described above, and NT refers to not tested.

The invention will now be described in reference to the following Examples. These Examples are not to be regarded as limiting the scope of the present invention, but shall only serve in an illustrative manner.

Examples

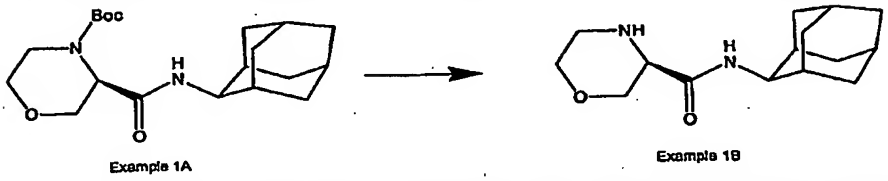
Example 1A (R)-4-Boc-morpholine-3-carboxylic acid adamantan-2-ylamide



N-Boc-R-morpholinic acid Example 1A

N-Boc-R-morpholinic acid (500mg, 2.16 mmol), 2-adamantanamine-hydrochloride salt (188 mg, 2.59 mmol), HATU (986 mg, 2.59mmol) were placed in a round bottom flask and dried under high vacuum for 2 hours. DMF (10ml) and CH_2Cl_2 (10ml) were added to dissolve reagents, followed by the addition of triethylamine (1.21 ml, 8.64mmol), the resultant reaction mixture was stirred at room temperature overnight. The reaction solution was taken into 100 ml of 2:1 EtOAc:benzene, and washed with saturated $NaHCO_3$ (2x15 ml), brine (15ml), 0.2 N HCl solution (2x15ml), and brine (2x15 ml). The organic layer was dried over $MgSO_4$, and concentrated in vacuo. The product was purified by flash chromatography eluting with 20% EtOAc in CH_2Cl_2 to afford (R)-4-Boc -morpholine-3-carboxylic acid adamantan-2-ylamide (289 mg, 37%; LCMS: 365.2).

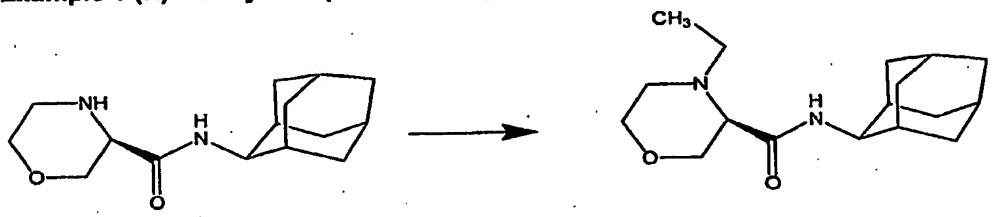
Example 1B (R)-morpholine-3-carboxylic acid adamantan-2-ylamide



Example 1A Example 1B

(R)-4-Boc -morpholine-3-carboxylic acid adamantan-2-ylamide (289mg) was dissolved in neat TFA (5 ml) and stirred at room temperature for 1 hour. The reaction solution was then concentrated in vacuo. The resultant gummy solid was tritiated with anhydrous diethyl ether to afford (R)-morpholine-3-carboxylic acid adamantan-2-ylamide trifluoroacetic acid salt (300mg, 100%; LCMS: 265.1).

Example 1 (R)-4-Ethyl-morpholine-3-carboxylic acid adamantan-2-ylamide

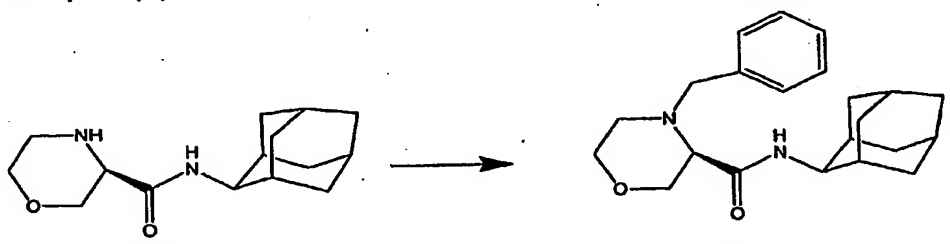


Example 1 B Example 1

(R)-Morpholine-3-carboxylic acid 2-adamantanamine amide trifluoroacetic acid salt (74 mg) was dissolved in DMF (1 ml), followed by the addition of Et_3N (60.1 µl) and EtI (32 µl), and the reaction solution was stirred at room temperature for 7h. EtI (64 µl) and DMF (1ml) were added, and the reaction solution was stirred at room temperature overnight. The reaction mixture was diluted with 2:1 of EtOAc:benzene (50 ml), washed with saturated with $NaHCO_3$ (10 ml), brine (2x10 ml). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The product was pumped under high vacuum overnight. The product was then converted to its HCl salt by dissolving in MeOH (2 ml), followed by the addition of 1 M HCl in ether (0.5 ml) to afford (R)-4-ethyl-morpholine-3-carboxylic acid adamantan-2-ylamide hydrochloride salt (55 mg, 86%).

^{1}H NMR (400 MHz, MeOD) δ ppm 1.05 - 1.14 (3 H, m) 1.68 (2 H, d, *J*=12.13 Hz) 1.79-1.93 (12 H, m) 2.19 - 2.29 (2 H, m) 2.67 (1 H, dq, *J*=12.41, 7.40 Hz) 2.94 - 3.04 (2 H, m) 3.46 (1 H, dd, *J*=11.24, 9.73 Hz) 3.62 (1 H, td, *J*=11.31, 2.40 Hz) 3.80 - 3.88 (2 H, m) 3.96 (1 H, s). LCMS (M+1): 293.

Example 2 (R)- 4-Benzyl-morpholine-3-carboxylic acid adamantan-2-ylamide



Example 1B Example 2

(R)-Morpholine-3-carboxylic acid 2-adamantanamine amide trifluoroacetic acid salt (88.9 mg) was dissolved in DMF (1ml), followed by the addition of Et_3N (197 µl) and benzyl chloride (135 µl), and the reaction solution was stirred at room overnight. The reaction mixture was diluted with 2:1 of EtOAc:benzene (50 ml), washed with saturated with $NaHCO_3$ (2x5 ml), brine (5 ml), saturated NH_4Cl solution (2x5ml), and brine (5ml). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The product was purified by flash chromatography eluting with CH_2Cl_2. The free basic product was then converted to its HCl salt by dissolving in MeOH (2 ml), followed by the addition of 1 M HCl in ether (0.5 ml) to afford (R)-4-benzyl-morpholine-3-carboxylic acid adamantan-2-ylamide hydrochloride salt (64 mg, 70%). ^1H NMR (400 MHz, MeOD) δ ppm 1.57 (1 H, d, *J*=12.13 Hz) 1.66 (1 H, dd, *J*=12.13, 1.77 Hz) 1.74 - 1.84 (9 H, m) 1.89 (1 H, s) 2.25 (1 H, ddd, *J*=12.06, 10.55, 3.41 Hz) 2.73-2.78 (1 H, m) 3.07 (1 H, dd, *J*=9.35, 3.54 Hz) 3.28 (2 H, td, *J*=3.60, 2.40 Hz) 3.50 - 3.60 (2 H, m) 3.67 - 3.77 (1 H, m) 3.85 (1 H, s) 3.86 - 3.91 (1 H, m) 3.96 (1 H, s) 4.85 (2H, s) 7.27 - 7.36 (5 H, m). LCMS (M+1): 355.

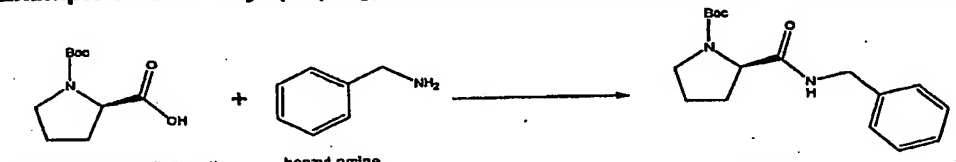
Example 3 (R)-4-methyl-morpholine-3-carboxylic acid adamantan-2-ylamide

Example 1B Example 3

(R)-Morpholine-3-carboxylic acid adamantan-2-ylamide trifluoroacetic acid salt (106 mg) was dissolved in $CHCl_3$ (5 ml) and THF (5 ml), followed by the addition of formaldehyde (110 µl) and formic acid (42.9 µl), the reaction mixture was heated to

reflux overnight. To the reaction mixture was added EtOAc 9100 ml) and saturated $NaHCO_3$ (20 ml). The organic layer was washed brine (2x10ml), dried over $MgSO_4$ and concentrated in vacuo to afford (R)-4-methyl-morpholine-3-carboxylic acid adamantan-2-ylamide which was then converted to the corresponding HCl salt (70 mg, 80%; LCMS: 279.2).

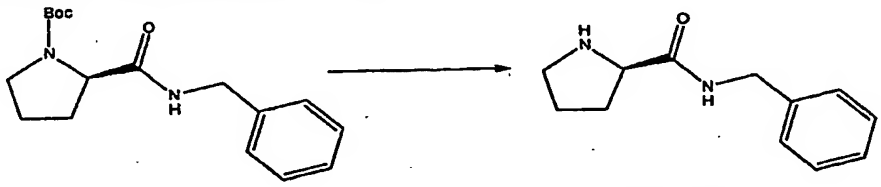
Example 3A *tert*-butyl-(2*R*)-2-[(benzylamino)carbonyl]pyrrolidine-1-carboxylate



N-(tert-butoxycarbonyl)-D-proline benzyl amine Example 3A

N-(tert-butoxycarbonyl)-D-proline (500 mg, 2.32 mmol) was placed in a round bottom flask. DMAP (14 mg, 0.12 mmol) in 2.3 mL CH_2Cl_2, HOBt (345 mg, 2.55 mmol) in 6.0 mL CH_2Cl_2, benzyl amine (380 uL, 3.48 mmol), EDC (489 mg, 2.55 mmol) in 6.0 mL CH_2Cl_2, and NMM (510 uL, 4.64 mmol) were added, respectively, to the flask. The resultant mixture was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and the residue was partitioned between EtOAc (400 mL) and 0.5 N HCl (40 mL). The organic layer was separated and washed with 0.5 N HCl(40 mL), brine (40 mL), saturated $NaHCO_3$ (2 x 40 mL), brine (40 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography eluting with hexanes/EtOAc (20-45%) to afford the title compound (630 mg, 89% yield). ^1H NMR (400 MHz, DMSO-D6) δ ppm 1.23 - 1.31 (6 H, m) 1.40 (3 H, s) 1.72 - 1.84 (3 H, m) 2.04 –2.16 (1 H, m) 3.24 - 3.33 (2 H, m) 3.36 - 3.44 (1 H, m) 4.04 - 4.12 (1 H, m) 4.12 - 4.23 (1 H, m) 4.29 - 4.37 (1 H, m) 7.27 (5 H, td, *J*=14.84, 7.96 Hz) 8.37 (1 H, s); LCMS (M+1): 305.

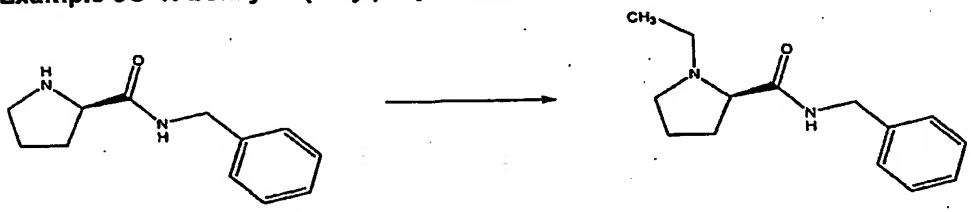
Example 3B N-benzyl-D-prolinamide



Example 3A Example 3B

To a cooled (0-5°C) solution of *tert*-butyl-(2*R*)-2-[(benzylamino)carbonyl]pyrrolidine-1-carboxylate (560 mg, 1.84 mmol) in CH_2Cl_2 (9 mL) was added TFA (9 mL). After 2 hours, the solution was concentrated in vacuo. The residue was azeotroped with toluene (2 x 10 mL) then placed under high vacuum overnight to afford the title compound as the TFA salt (776 mg).^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.95 (3 H, s) 2.34 (1 H, d, *J*=6.82 Hz) 3.31 (2 H, s) 4.32 - 4.42 (2 H, m) 4.60 (1 H, s) 7.15 - 7.24 (3 H, m) 7.26 - 7.32 (2 H, m) 7.58 (1 H, s) 8.08 (1 H, t, *J*=4.93 Hz) 10.72 (1 H, s); LCMS (M+1): 305.

Example 3C N-benzyl-1-(ethyl)-D-prolinamide

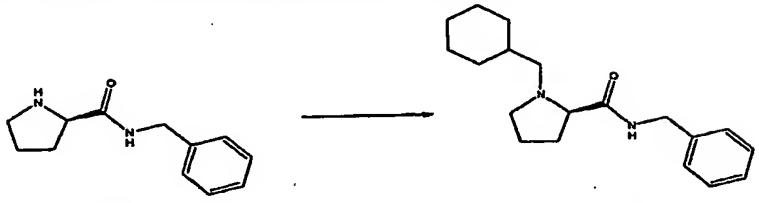


Example 3B

Example 3C

To a solution of N-benzyl-D-prolinamide (115 mg, 0.361 mmol) in DMF (1 mL) was added TEA (151 uL, 1.08 mmol) followed by 1-iodo-ethane (44 uL, 0.54 mmol). The resultant solution was subjected to microwave conditions for 20 minutes at 100°C. The reaction mixture was diluted with 2:1 EtOAc/benzene (100 mL). The organic solution was washed with saturated $NaHCO_3$ (2 x 10 mL), brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (0-10%) containing 2% NH_3 (28% in H_2O) to afford an orange oil. To a solution of the oil in MeOH (2 mL) was added HCl (1M in diethyl ether, 2.2 mL). The solution was stirred at room temperature for 40 minutes then concentrated in vacuo to afford the title compound as the HCl salt (40 mg, 41% yield). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 1.14 - 1.25 (3 H, m) 1.82 - 1.93 (2 H, m) 1.97 - 2.09 (1 H, m) 3.10 - 3.22 (3 H, m) 3.60 (1 H, d, J=5.05 Hz) 4.17 (1 H, s) 4.29 - 4.39 (2 H, m) 7.24 - 7.29 (3 H, m) 7.31 - 7.36 (2 H, m) 9.32-9.45 (1 H, m) 9.51 (1 H, s); LCMS (M+1): 233.

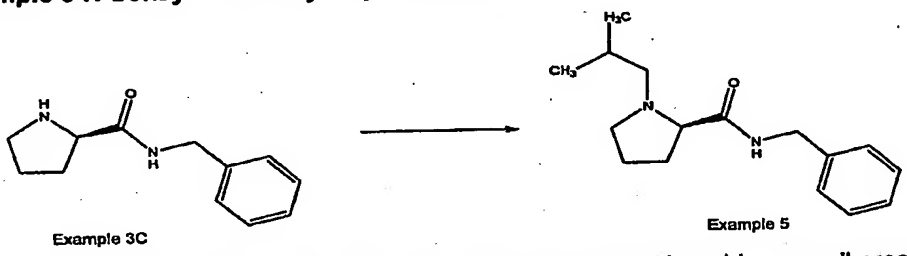
Example 4 N-benzyl-1-(cyclohexylmethyl)-D-prolinamide



Example 3C Example 4

To a solution of N-benzyl-D-prolinamide (133 mg, 0.314 mmol) in DMF (3.5 mL) was added TEA (137 uL, 0.979 mmol) and cyclohexylmethyl bromide (75 uL, 0.54 mmol). The resultant solution was stirred at room temperature for 2.5 hours. Additional TEA (0.20 mL, 1.4 mmol) and cyclohexylmethyl bromide (0.10 mL, 0.72 mmol) was added and the resultant solution was heated to 100°C and stirred overnight. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by flash chromatography eluting with hexanes/EtOAc (20-50%) to afford the title compound (39 mg, 42% yield). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.54-0.65 (1 H, m) 0.69-0.80 (1 H, m) 1.03-1.34 (5 H, m) 1.52-1.87 (6 H, m) 1.98-2.09 (2 H, m) 2.13-2.31 (3 H, m) 2.84-2.93 (1H, m) 3.05 (1 H, s) 4.15-4.40 (2 H, m) 7.23 (3 H, d, *J*=6.06 Hz) 7.29 (2 H, d, *J*=6.57 Hz) 7.95 (1 H, s); LCMS (M+1): 301.

Example 5 N-benzyl-1-isobutyl-D-prolinamide

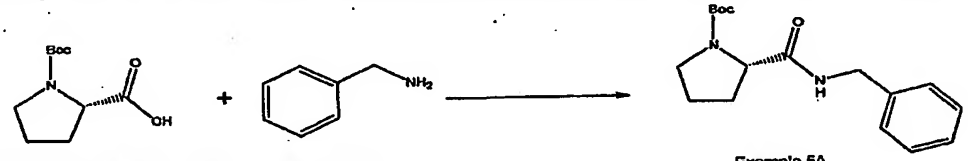


Example 3C Example 5

N-benzyl-D-prolinamide (150 mg, 0.471 mmol) was placed in a small pressure tube. DMF (5 mL) was added to dissolve the substrate followed by TEA (196 uL, 1.41 mmol) and 1-iodo-2-methyl-propane (109 uL, 0.943 mmol). The tube was sealed and the solution was heated to 50°C overnight. The solution was cooled to room temperature and concentrated in vacuo. The residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (0-10%) to afford an oil. To a solution of the resultant oil in MeOH (2 mL) was added HCl (1M in diethyl ether, 2.8 mL). The solution was stirred for 40 min at room temperature then concentrated in vacuo to

afford the title compound as the HCl salt (70mg, 50% yield). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.90 (3 H, d, *J*=6.57 Hz) 0.96 (3 H, d, *J*=6.57 Hz) 1.84 - 1.96 (3 H, m) 2.01-2.12- (1 H, m) 3.00 (2 H, s) 3.12 - 3.23 (1 H, m) 3.63-3.74 (1 H, m) 4.18 - 4.27 (1 H, m) 4.31 - 4.41 (2 H, m) 7.23 - 7.35 (5 H, m) 9.10 (1 H, s) 9.55 (1H, s); LCMS (M+1): 301.

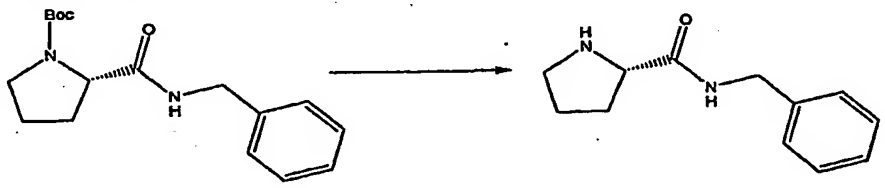
Example 5A *tert*-butyl-(2*S*)-2-[(benzylamino)carbonyl]pyrrolidine-1-carboxylate



N-(tert-butoxycarbonyl)-L-proline benzyl amine Example 5A

N-(tert-butoxycarbonyl)-L-proline (500 mg, 2.32 mmol) was placed in a round bottom flask. DMAP (14 mg, 0.12 mmol) in 2.3 mL CH_2Cl_2, HOBt (345 mg, 2.55 mmol) in 6.0 mL CH_2Cl_2, benzyl amine (380 uL, 3.48 mmol), EDC (489 mg, 2.55 mmol) in 6.0 mL CH_2Cl_2, and NMM (510 uL, 4.64 mmol) were added, respectively, to the flask. The resultant mixture was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and the residue was partitioned between EtOAc (400 mL) and 0.5 N HCl (40 mL). The organic layer was separated and washed with 0.5 N HCl (40 mL), brine (40 mL), saturated $NaHCO_3$ (2 x 40 mL), brine (40 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography eluting with hexanes/EtOAc (20-50%) to afford the title compound (647 mg, 92% yield). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 1.23 - 1.31 (6 H, m) 1.40 (3 H, s) 1.72 - 1.84 (3 H, m) 2.04 –2.16 (1 H, m) 3.24 - 3.33 (2 H, m) 3.36 - 3.44 (1 H, m) 4.04 - 4.12 (1 H, m) 4.12 - 4.23 (1 H, m) 4.29 - 4.37 (1 H, m) 7.27 (5 H, td, *J*=14.84, 7.96 Hz) 8.37 (1 H, s); LCMS (M+1): 305.

Example 5B N-benzyl-L-prolinamide

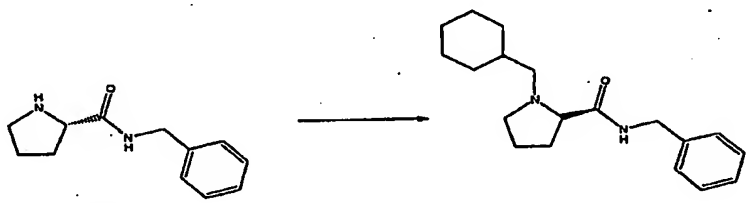


Example 5A Example 5B

To a cooled (0-5°C) solution of *tert*-butyl-(2*S*)-2-[(benzylamino)carbonyl]pyrrolidine-1-carboxylate (580 mg, 1.91 mmol) in CH_2Cl_2 (9

mL) was added TFA (9 mL). After 2 hours, the solution was concentrated in vacuo. The residue was azeotroped with toluene (2 x 10 mL) then placed under high vacuum overnight to afford the title compound as the TFA salt (721 mg). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.95 (3 H, s) 2.34 (1 H, d, *J*=6.82 Hz) 3.31 (2 H, s) 4.32 - 4.42 (2 H, m) 4.60 (1 H, s) 7.15 - 7.24 (3 H, m) 7.26 - 7.32 (2 H, m) 7.58 (1 H, s) 8.08 (1 H, t, *J*=4.93 Hz) 10.72 (1 H, s); LCMS (M+1): 305.

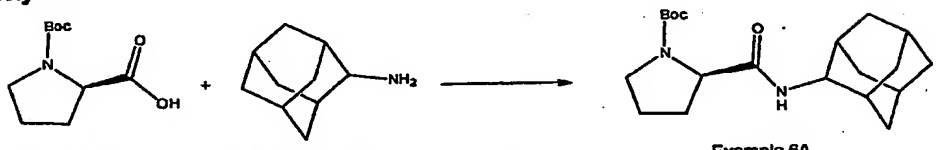
Example 6 N-benzyl-1-(cyclohexylmethyl)-L-prolinamide



Example 5B Example 6

To a solution of N-benzyl-L-prolinamide (156 mg, 0.490 mmol) in DMF (4.0 mL) was added TEA (237 uL, 1.96 mmol) and cyclohexylmethyl bromide (136 uL, 0.979 mmol). The resultant solution was heated to 100°C for 6 hours. The reaction mixture was cooled to room temperature overnight then diluted with 2:1 EtOAc/benxene (200 mL). The organic solution was washed with 0.5 N HCl (2 x 40mL), brine (40 mL), saturated $NaHCO_3$ (2 x 40 mL), brine (40 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 31 mg product. The combined aqueous layers were concentrated in vacuo. The residue was partitioned between EtOAc (200 mL) and H_2O (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (200 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 51 mg crude product. These two batches of crude product were combined and purified by flash chromatography (2x) eluting with hexanes/EtOAc (20-50%) to afford the title compound (48 mg, 33% yield). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.54-0.65 (1 H, m) 0.69-0.80 (1 H, m) 1.03-1.34 (5 H, m) 1.52-1.87 (6 H, m) 1.98-2.09 (2 H, m) 2.13-2.31 (3 H, m) 2.84-2.93 (1H, m) 3.05 (1 H, s) 4.15-4.40 (2 H, m) 7.23 (3 H, d, *J*=6.06 Hz) 7.29 (2 H, d, *J*=6.57 Hz) 7.95 (1 H, s); LCMS (M+1): 301.

Example 6A *tert*-butyl-(2*R*)-2-[(2-adamantylamino)carbonyl]pyrrolidine-1-carboxylate



N-(tert-butoxycarbonyl)-D-proline 2-adamanyl amine Example 6A

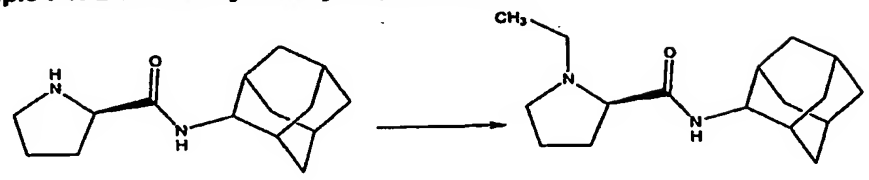
N-(tert-butoxycarbonyl)-D-proline (1.00g, 5.65 mmol), EDC (982 mg, 5.12 mmol), HOBt (692 mg, 5.12 mmol), DMAP (28 mg, 0.23 mmol), and 2-adamanyl amine hydrochloride (1.31 g, 6.98 mmol) were charged into a round bottom flask. CH_2Cl_2 (25 mL) was added to dissolve the reagents followed by NMM (1.02 mL, 9.3 mL). The resultant solution was stirred at room temperature overnight. The solution was concentrated in vacuo and the residue was partitioned between EtOAc (400 mL) and 0.5 N HCl (40 mL). The organic layer was separated and washed with 0.5 N HCl (40 mL), brine (40 mL), saturated $NaHCO_3$ (2 x 40 mL), brine (40 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography eluting with hexanes/EtOAc (0-50%) to afford the title compound (1.6 g, 99% yield). ^1H NMR (400 MHz, DMSO-D6) δ ppm 1.28 - 1.40 (9 H, m) 1.48 (2 H, d, *J*=12.38 Hz) 1.65-1.72 (4 H, m) 1.72 - 1.83 (11 H, m) 1.93-2.01 (1 H, m) 2.02 - 2.13 (1 H, m) 3.22 - 3.29 (1 H, m) 3.75 - 3.85 (1 H, m) 4.17 - 4.25 (1 H, m) 7.62 (1 H, d, *J*=7.58 Hz); LCMS (M+1): 349.

Example 6B N-2-adamantyl-D-prolinamide

Example 6A Example 6B

To a solution of *tert*-butyl-(2*R*)-2-[(2-adamantylamino)carbonyl]pyrrolidine-1-carboxylate (1.57 g, 4.51 mmol) in CH_2Cl_2 (5 mL) was added TFA (5 mL). The resultant solution was stirred at room temperature for 3 hours. The reaction mixture was concentrated, azeotroped with toluene, then triturated with diethyl ether to afford the title compound as the TFA salt (2.09 g). ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.51 (2 H, d, *J*=12.63 Hz) 1.69 (2 H, s) 1.74 – 2.01 (13 H, m) 2.26 - 2.35 (1 H, m) 3.22 (2 H, ddd, *J*=17.62, 11.43, 6.06 Hz) 3.87 (1 H, d, *J*=6.82 Hz) 4.19 - 4.27 (1 H, m) 8.29 - 8.37 (1 H, m) 8.47 (1 H, s) 9.36 (1 H, s); LCMS (M+1): 249.

Example 7 N-2-adamantyl-1-ethyl-D-prolinamide

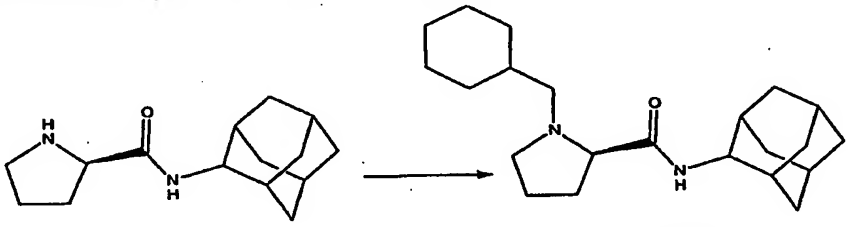


Example 6B

Example 7

To a solution of N-2-adamantyl-D-prolinamide (300 mg, 0.828 mmol) in DMF (2 mL) was added TEA (577 uL, 4.14 mmol) followed by 1-iodoethane (134 uL, 1.66 mmol). The resultant solution was subjected to microwave conditions for 20 minutes at 100°C. The reaction mixture was diluted with MTBE (200 mL). The organic solution was washed with saturated $NaHCO_3$ (3 x 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was dissolved in MeOH (10 mL), filtered through Celatom FW-50 and activated carbon (Darco G-60, -100 mesh powder), and concentrated in vacuo. To a cooled (0-5°C) solution of the crude product in MeOH (5 mL) was added HCl (1M in diethyl ether, 5.5 mL). The resultant solution was stirred for 30 min at room temperature then concentrated in vacuo. The residue was triturated with diethyl ether to afford the title compound as the HCl salt (173 mg, 67% yield). ^{1}H NMR (DMSO-D6) δ ppm 1.09 - 1.18 (3 H, m) 1.50 (2 H, d, *J*=12.38 Hz) 1.72 - 1.84 (10 H, m) 1.95 - 2.06 (4 H, m) 2.40 - 2.47 (1 H, m) 3.09 - 3.20 (4 H, m) 3.54 - 3.64 (1 H, m) 3.89 (1 H, d, *J*=7.33 Hz) 4.28 (1 H, q, *J*=7.83 Hz) 8.78 (1H, d, *J*=7.07 Hz) 9.42 (1 H, s); LCMS (M+1): 277.

Example 8 N-2-adamantyl-1-(cyclohexylmethyl)-D-prolinamide



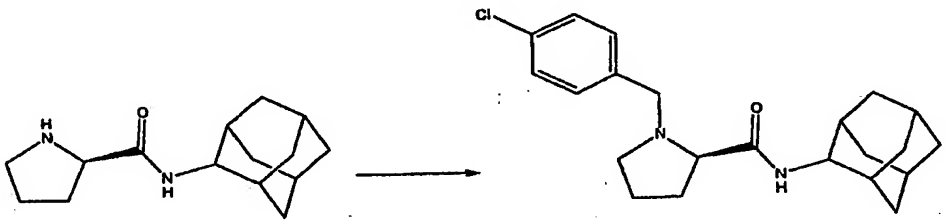
Example 6B

Example 8

To a solution of N-2-adamantyl-D-prolinamide (300 mg, 0.828 mmol) in DMF (2 mL) was added TEA (577 uL, 4.14 mmol) followed by cyclohexylmethyl bromide (229 uL, 1.66 mmol). The resultant solution was subjected to microwave conditions for 20 minutes at 100°C. Additional TEA (577 uL, 4.14 mmol) and cyclohexylmethyl

bromide (229 uL, 1.66 mmol) was added and the reaction mixture was subjected to microwave conditions for 20 minutes at 100°C. The reaction mixture was diluted with MTBE (200 mL). The organic solution was washed with saturated $NaHCO_3$ (3 x 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The product was purified by flash chromatography eluting with CH_2Cl_2/MeOH (3%) followed by preparative HPLC purification to afford the title compound as the TFA salt (24 mg, 6% yield). ^1H NMR (400 MHz, DMSO-D6) δ ppm 0.86 – 0.96 (2 H, m) 1.04 – 1.19 (3 H, m) 1.50-1.99 (21 H, m) 1.99 - 2.03 (1 H, m) 2.39 - 2.48 (2 H, m) 2.93 - 3.03 (2 H, m) 3.16 (1 H, dd, *J*=10.86, 7.83 Hz) 3.65 – 3.72 (1 H, m) 3.88 (1 H, d, *J*=6.82 Hz) 4.12 (1 H, q, *J*=8.00 Hz) 8.51 (1 H, d, *J*=7.07 Hz) 8.98 (1 H, s); LCMC (M+1): 345.

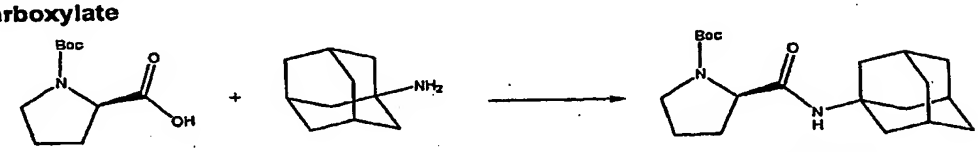
Example 9 N-2-adamantyl-1-(4-chlorobenzyl)-D-prolinamide



Example 6B Example 9

To a solution of N-2-adamantyl-D-prolinamide (300 mg, 0.828 mmol) in DMF (2 mL) was added TEA (577uL, 4.14 mmol) followed by 4-chlorobenzylchloride (267 mg, 1.66 mmol). The resultant solution was subjected to microwave conditions for 20 minutes at 100°C. The reaction mixture was diluted with MTBE (200 mL). The organic solution was washed with saturated $NaHCO_3$ (3 x 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was dissolved in MeOH (10 mL), filtered through Celatom FW-50 and activated carbon (Darco G-60, -100 mesh powder), and concentrated in vacuo. To a cooled (0-5°C) solution of the crude product in MeOH (5 mL) was added HCl (1M in diethyl ether, 5.5 mL). The resultant solution was stirred for 30 min then concentrated in vacuo. The residue was triturated with diethyl ether to afford the title compound as the HCl salt (45 mg, 13% yield). ^1H NMR (400 MHz, DMSO-D6) δ ppm 0.79 - 0.89 (1 H, m) 1.24-1.47 (2 H, d, *J*=19.20 Hz) 1.63 - 1.94 (10 H, m) 2.00-2.11 (1 H, m) 3.22-3.42 (4H, m) 3.56-3.67 (2H, m) 4.34 (2 H, dd, *J*=11.87, 7.83 Hz) 4.39 - 4.47 (1 H, m) 7.41 - 7.47 (2 H, m) 7.48 - 7.54 (2 H, m) 8.42 (1 H, d, *J*=7.58 Hz) 9.64 (1 H, s); LCMS (H+1): 373.

Example 9A *tert*-butyl-(2*R*)-2-[(1-adamantylamino)carbonyl]pyrrolidine-1-carboxylate



N-(tert-butoxycarbonyl)-D-proline 1-adamantyl amine Example 9A

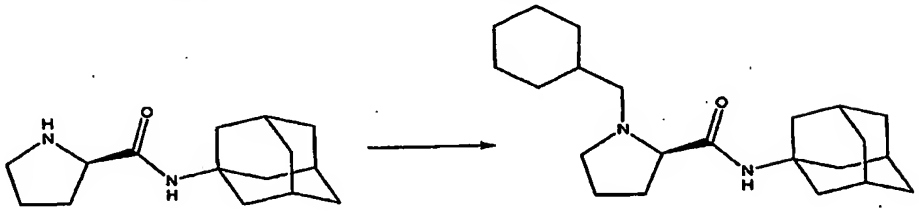
N-(*tert*-butoxycarbonyl)-D-proline (1.00g, 5.65 mmol), EDC (982 mg, 5.12 mmol), HOBt (692 mg, 5.12 mmol), DMAP (28 mg, 0.23 mmol), and 1-adamanyl amine (1.06 g, 6.98 mmol) were charged into a round bottom flask. CH_2Cl_2 (25 mL) was added to dissolve the reagents followed by NMM (1.02 mL, 9.3 mL). The resultant solution was stirred at room temperature overnight. The solution was concentrated in vacuo and the residue was partitioned between EtOAc (400 mL) and 0.5 N HCl (40 mL). The organic layer was separated and washed with 0.5 N HCl (40 mL), brine (40 mL), saturated $NaHCO_3$ (2 x 40 mL), brine (40 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography eluting with hexanes/EtOAc (5-50%) to afford the title compound (1.7g, 105% yield). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 1.32 - 1.39 (10 H, m) 1.56 - 1.64 (6 H, m) 1.66 - 1.80 (3 H, m) 1.87 - 1.94 (6 H, s) 1.96 - 2.07 (4 H, m) 3.20 - 3.28 (1 H, m) 3.94 - 4.05 (1 H, m) 7.21 (1 H, s); LCMS (M+1): 349.

Example 9B N-1-adamantyl-D-prolinamide

Example 9A Example 9B

To a solution of *tert*-butyl-(2*R*)-2-[(1-adamantylamino)carbonyl]pyrrolidine-1-carboxylate, (1.64g 4.71 mmol) in CH_2Cl_2 (5 mL) was added TFA (5 mL). The resultant solution was stirred at room temperature for 3 hours. The reaction mixture was concentrated in vacuo. The residue was azeotroped with toluene then triturated with diethyl ether to afford the title compound as the TFA salt (2.25 g). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.60 - 1.70 (6 H, m) 1.94 - 2.01 (8 H, m) 2.05 (3 H, s) 2.34 - 2.45 (1 H, m) 3.38 (2 H, t, *J*=6.44 Hz) 4.52 (1 H, dd, *J*=7.83, 5.81 Hz) 7.35 (1 H, s); LCMS (M+1): 249.

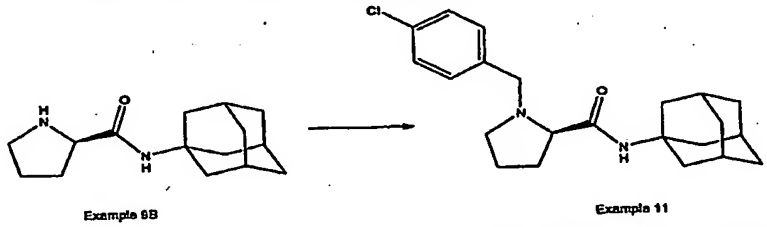
Example 10 N-1-adamantyl-1-(cyclohexylmethyl)-D-prolinamide



Example 9B Example 10

To a solution of N-1-adamantyl-D-prolinamide (300 mg, 0.828 mmol) in DMF (2 mL) was added TEA (577 uL, 4.14 mmol) followed by cyclohexylmethyl bromide (229 uL, 1.66 mmol). The resultant solution was subjected to microwave conditions for 20 minutes at 100°C. The reaction mixture was diluted with MTBE (200 mL). The organic solution was washed with saturated $NaHCO_3$ (3 x 20 mL), brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. To a cooled (0-5°C) solution of the residue in MeOH (5 mL) was added HCl (1M in diethyl ether, 3 mL). The resultant solution was stirred for 30 min then concentrated in vacuo. The residue was triturated with diethyl ether to afford the title compound as the HCl salt (95 mg, 31% yield). ^1H NMR (400 MHz, DMSO-D6) δ ppm 0.84 - 0.96 (2 H, m) 1.10 - 1.22 (3 H, m) 1.50 - 1.69 (10 H, m) 1.71 - 1.98 (10 H, m) 2.02 (4 H, s) 2.36 - 2.47 (1 H, m) 2.96 (2 H, m) 3.14 (1 H, dt, *J*=18.63, 8.12 Hz) 3.61 - 3.72 (1 H, m) 3.91 – 4.04 (2 H, m) 8.42 (1 H, s) 8.91 (1 H, s); LCMS (H+1): 345.

Example 11 N-1-adamantyl-1-(4-chlorobenzyl)-D-prolinamide

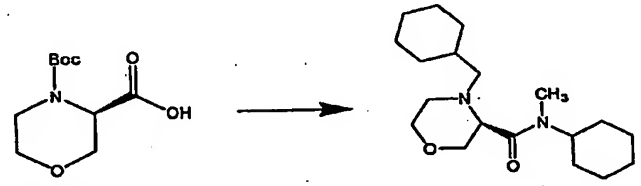


Example 9B Example 11

To a solution of N-1-adamantyl-D-prolinamide (300 mg, 0.828 mmol) in DMF (2 mL) was added TEA (577 uL, 4.14 mmol) followed by and 4-chlorobenzyl chloride (267 mg, 1.66 mmol). The resultant solution was subjected to microwave conditions for 20 minutes at 100°C. The reaction mixture was diluted with MTBE (200 mL). The organic solution was washed with saturated $NaHCO_3$ (3 x 20 mL) and brine (20 mL),

dried ($MgSO_4$), filtered, and concentrated in vacuo. The product was purified by preparative HPLC to afford the title compound as the TFA salt (55 mg, 14% yield). ^1H NMR (400 MHz, DMSO-D6) δ ppm 1.51 - 1.61 (6 H, m) 1.68 (6 H, d, *J*=1.26 Hz) 1.70 - 1.86 (2 H, m) 1.95 (3 H, s) 2.00 - 2.10 (1 H, m) 2.32 - 2.42 (1 H, m) 3.21 –3.31 (1 H, m) 3.55 – 3.64 (1 H, m) 3.93 - 4.03 (1 H, m) 4.24 - 4.32 (1 H, m) 4.40 (1 H, d, *J*=12.63 Hz) 7.44 - 7.50 (4 H, m) 7.87 (1 H, s) 9.50 (1 H, s); LCMC (M+1): 373.

Example 12 (3*R*)-*N*-cyclohexyl-4-(cyclohexylmethyl)-*N*-methylmorpholine-3-carboxamide



(R)-4-Boc-Morpholine-3-carboxylic acid Example 12

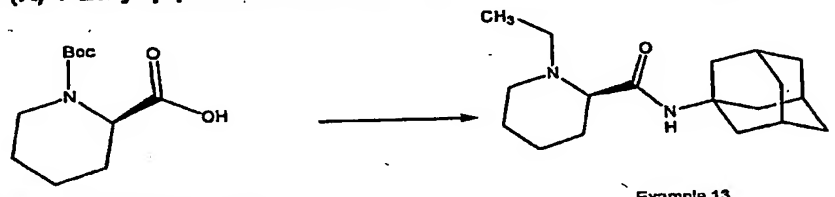
(R)-4-Boc-Morpholine-3-carboxylic acid (508.7mg – 2.2 mmol) was reacted with N-Methylcyclohexylamine (249mg) in a 1:1 ratio at room temperature overnight in the presence of 1.2 equivalent of HATU (O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) and 1.2 equivalent of TEA (Trimethylamine) using NMP (4-Methylmorpholine) as the solvent. The reaction was worked up using EtOAc and H_2O. The EtOAc layer was dried with Na_2SO_4, concentrated, and purified by normal phase (using Biotage column) using EtOAc and Hexane. The intermediate was deprotected using 1:1 TFA:Methylene chloride overnight. The solvent was evaporated and the crude product was washed three times with n-Heptane. The crude material was then reacted with 1 equivalent (296.1mg) of cyclohexanecarboxaldehyde in the presence of 2.4 equivalents of $NaHB(OAc)_3$ with CH_3CN as solvent and allowed to stir overnight. The reaction was then concentrated to dryness and worked up using EtOAc and H_2O. The EtOAc layer was dried using Na_2SO_4, concentrated, and purified using reverse phase (with 0.1%HOAc in H_2O and CH_3CN as buffer/solvent). The purified product was a syrup (638.8mg, 90% yield).^{13}C NMR (75.47 MHz, CD_3CN) δ ppm 19.38, 24.67, 24.81, 24.97, 24.99, 25.05, 25.24, 25.30, 25.54, 25.60, 26.18, 26.60, 28.51, 28.68, 28.96, 28.99, 30.51, 30.63, 30.73, 30.92, 31.32, 34.20, 34.27, 50.46, 50.70, 52.46, 55.26, 61.31, 61.68, 65.74, 66.01, 66.79, 67.86, 168.64, 168.93. Data was acquired on a Bruker DRX 300 NMR Spectrometer using a broadband decoupling scheme to decouple the protons from the carbons.

Purification Conditions included a Waters Bondapak column C18, 37-55 micron (particle size), 47x300mm (column size) having a flow rate of 75mL/min, a detector of UV 220nm, where Buffer A is: 0.1%HOAc in H_2O and Buffer B0.1%HOAc in CH_3CN.

The column was equilibrated in A for 20 minutes. The sample was dissolved in 10ml of DMSO, filtered, and injected onto the column. The gradient was held at 100%A for 5 minutes and then increased linearly to 90%A/10%B in 20 minutes and then held at 10%B for another 25 minutes. The desired product came out at 26 minutes during the isocratic hold of the gradient. The fractions were checked, pooled, and lyophilized to afford a syrup.

The LC/MS retention time was 5.5 min. The column was Phenomenex Synergi MAX-RP. The particle size was 4 micron. The gradient started with 90%A/10%B and increased linearly to 10%A/90%B in 12 min. (w/ A=0.1%HOAc in H2O and B=0.1%HOAc in CH3CN). LCMC (M+1): 323.

Example 13 (R)-1-Ethyl-piperidine-2-carboxylic acid adamantan-1-ylamide



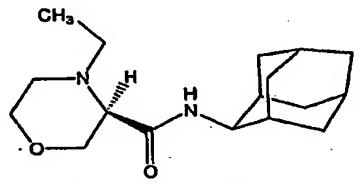
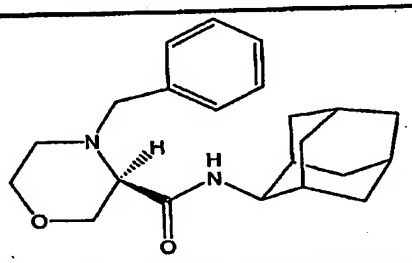
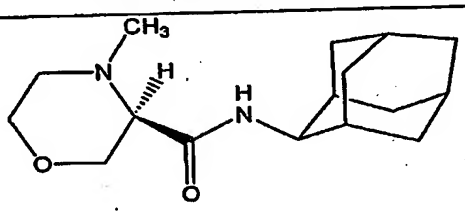
(R)-4-Boc-Morpholine-3-carboxylic acid

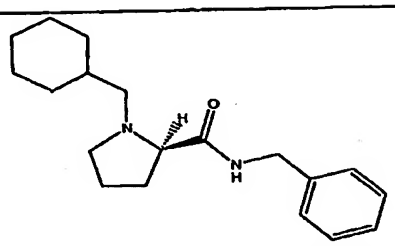
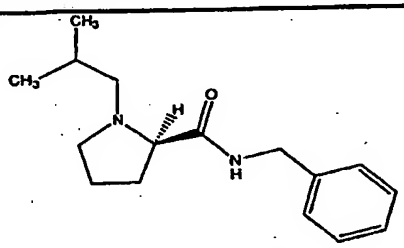
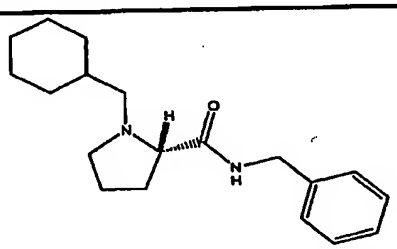
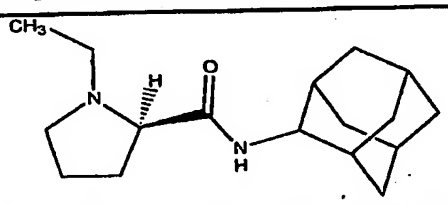
Example 13

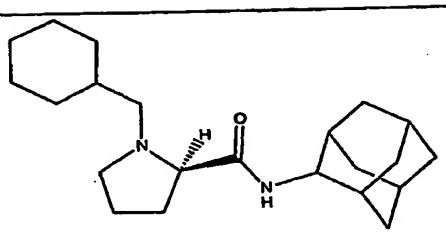
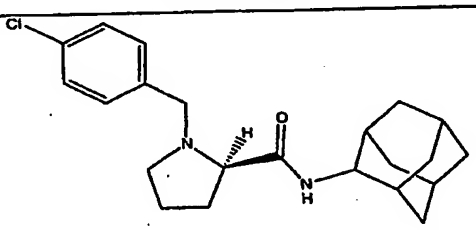
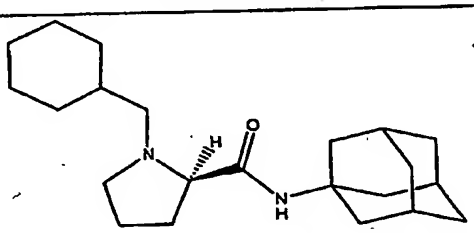
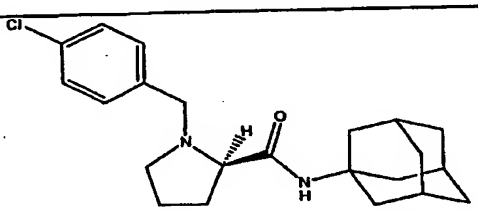
A mixture of admantan-1-ylamine (230 mg, 1.52 mmol), (R)-*N*-Bochomoproline (290 mg, 1.26 mmol), HATU (719 mg, 1.89 mmol), triethylamine (0.35 mL) in DMF (5 mL) was stirred overnight. The mixture was diluted with EtOAc and partioned between EtOAc and water. The organic layer was washed with brine, dried over sodium sulphate and concentrated to give a residue, which was purified by silica gel chromatography (10 to 20% EtOAc/Hexane) to give (R)-1-Boc-piperidine-2-carboxylic acid adamantan-1-ylamide as a white solid (387 mg, 85%). To a solution of the above amide (530 mg, 1.46 mmol) in CH_2Cl_2 (3 mL) was added HCl (4 N in dioxane, 8 mL). The mixture was stirred at 23 °C for 2 hours. The mixture was concentrated in vacuum to give (R)- piperidine-2-carboxylic acid adamantan-1-ylamide as a HCl salt (455 mg, 99%). To a mixture of the above HCl salt (150 mg, 0.572 mmol) in DMF (3 mL) was added EtI (69 uL, 0.858 mL) and K_2CO_3 (237 mg, 1.716 mmol). The mixture was stirred at 23 °C overnight. EtOAc was added. The mixture was portioned between EtOAc and water. The organic layer was washed with brine, dried over sodium

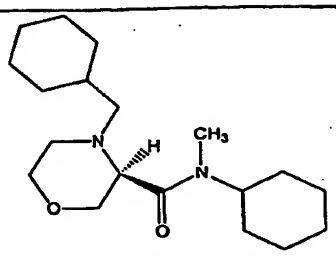
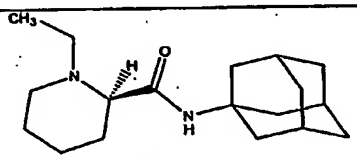
sulphate and concentrated to give the residue, which was purified by silica gel chromatography (50% EtOAc/Hexane) to give the title compound as a white solid (144 mg, 87%). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 1.20 (m, 3 H) 1.39 (d, J=9.60 Hz, 1 H) 1.68 (m, 11 H) 1.99 (m, 11 H) 2.98 (m, 3 H) 3.45 (m, 1 H) 3.66 (m, 1 H).

TABLE 1

Example Number	Ki (nM)	Structure IUPAC name	MS m/z	HPLC (min.)
1	2.1	 (R)-4-Ethyl-morpholine-3-carboxylic acid adamantan-2-ylamide	293	1.277
2	2.4	 (R)- 4-Benzyl-morpholine-3-carboxylic acid adamantan-2-ylamide	355	4.024
3	8	 (R)-4-methyl-morpholine-3-carboxylic acid adamantan-2-ylamide	279.2	2.722

4	15	 N-benzyl-1-(cyclohexylmethyl)-D-prolinamide	301	3.443
5	3.6	 N-benzyl-1-isobutyl-D-prolinamide	261	2.225
6	29% @100nM	 N-benzyl-1-(cyclohexylmethyl)-L-prolinamide	301	3.341
7	1.3	 N-2-adamantyl-1-ethyl-D-prolinamide	277	2.997

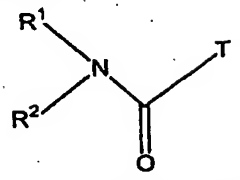
8	3.2	 N-2-adamantyl-1-(cyclohexylmethyl)-D-prolinamide	345	4.263
9	2.0	 N-2-adamantyl-1-(4-chlorobenzyl)-D-prolinamide	373	4.402
10	1.7	 N-1-adamantyl-1-(cyclohexylmethyl)-D-prolinamide	345	4.099
11	0.85	 N-1-adamantyl-1-(4-chlorobenzyl)-D-prolinamide	373	4.204

12	38.3	 **(3*R*)-*N*-cyclohexyl-4-(cyclohexylmethyl)-*N*-methylmorpholine-3-carboxamide**	323	5.5
13	14	 **(R)-1-Ethyl-piperidine-2-carboxylic acid adamantan-1-ylamide**	291.0	1.816

Various embodiments of the present invention have been described above but a person skilled in the art realizes further minor alterations that would fall into the scope of the present invention. The breadth and scope of the present invention should not be limited by any of the above-described exemplary embodiments, but should be defined only in accordance with the following claims and their equivalents.

We Claim:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein;

R^1 is $(C_1–C_6)$alkyl, $(CR^4R^5)_t(C_3-C_{12})$cycloalkyl, $(CR^4R^5)_t(C_6-C_{12})$aryl, or $(CR^4R^5)_t$(4-10)-membered heterocyclyl;

k is independently selected from 1 and 2;

j is independently selected from 0, 1, and 2;

t, u, p, q and v are each independently selected from 0, 1, 2, 3, 4, and 5;

T is a (4-10)-membered heterocyclyl containing at least one nitrogen atom and wherein said nitrogen atom is optionally substituted by R^3;

R^2 and R^3 are independently selected from H and $(C_1–C_6)$alkyl;

R^4 and R^5 are independently selected from H and (C_1-C_6)alkyl;

each carbon atom of T, R^1, R^2, and R^3 is optionally substituted by 1 or more R^6 groups;

each R^6 group is selected from the group consisting of halo, cyano, nitro, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, azido, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, $-(C=O)-R^7$, $-(C=O)-O-R^7$, $-O-(C=O)-R^7$, $-O-(C=O)-NR^7R^8$, $-NR^8(C=O)-R^9$, $-(C=O)-NR^8R^9$, $-NR^8R^9$, $-NR^8OR^9$, $-S(O)_kNR^8R^9$, $-S(O)_j(C_1-C_6)$alkyl, $-O-SO_2-R^9$, $-NR^8-S(O)_k-R^9$, $-(CR^{10}R^{11})_v(C_6-C_{12}$ aryl), $-(CR^{10}R^{11})_v(C_3-C_{12})$cycloalkyl, $-(CR^{10}R^{11})_v$(4-10)-membered heterocyclyl, $-(CR^{10}R^{11})_q(C=O)(CR^{10}R^{11})_v(C_6-C_{12})$aryl, $-(CR^{10}R^{11})_q(C=O)(CR^{10}R^{11})_v$(4-10)-membered heterocyclyl, $-(CR^{10}R^{11})_vO(CR^{10}R^{11})_q(C_6-C_{12})$aryl, $-(CR^{10}R^{11})_vO(CR^{10}R^{11})_q$(4-10)-membered heterocyclyl, $-(CR^{10}R^{11})_qS(O)_j(CR^{10}R^{11})_v(C_6-C_{12})$aryl, and $-(CR^{10}R^{11})_qS(O)_j(CR^{10}R^{11})_v$(4-10)-membered heterocyclyl;

any 1 or 2 carbon atoms of any (4-10)-membered heterocyclyl moiety of the foregoing R^6 groups are optionally substituted with an oxo group;

any carbon atom of a (C_1-C_6)alkyl, a (C_6-C_{12})aryl and a (4-10)-membered heterocyclyl of the foregoing R^6 groups are optionally substituted with 1 to 3 substituents independently selected from halo, cyano, nitro, $-CF_3$, $-CFH_2$, $-CF_2H$,

trifluoromethoxy, azido, $-OR^{12}$, $-(C=O)-R^{12}$, $-(C=O)-O-R^{12}$, $-O-(C=O)-R^{13}$, $-NR^{13}(C=O)-R^{13}$, $-(C=O)-NR^{14}R^{15}$, $-NR^{14}R^{15}$, $-NR^{14}OR^{15}$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, $-(CR^{16}R^{17})_u(C_6-C_{12})$aryl, and $-(CR^{16}R^{17})_u$(4-10)-membered heterocyclyl;

each R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} group is independently selected from H, $-(C_1-C_6)$alkyl, $-(C=O)NH(C_1-C_6)$alkyl, $-(CR^{18}R^{19})_p(C_6-C_{12})$aryl, and $-(CR^{18}R^{19})_p$(4-10)-membered heterocyclyl;

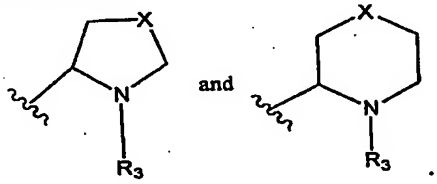
any 1 or 2 carbon atoms of the (4-10)-membered heterocyclyl of said each R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17}group is optionally substituted with an oxo group;

any carbon atoms of a (C_1-C_6)alkyl, a (C_6-C_{12})aryl, and a (4-10)-membered heterocyclyl of the foregoing R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} groups are optionally substituted with 1 to 3 substituents independently selected from halo, cyano, nitro, $-NR^{20}R^{21}$, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, and (C_1-C_6) alkoxy;

each R^{18}, R^{19}, R^{20}, and R^{21} group is independently selected from H and (C_1-C_6)alkyl;

and wherein any of the above-mentioned substituents comprising a $-CH_3$ (methyl), $-CH_2$ (methylene), or -CH (methine) group which is not attached to a halo, -SO or $-SO_2$ group or to a N, O or S atom optionally bears on said group a substituent independently selected from hydroxy, halo, $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkoxy, $-NH_2$, $-NH(C_1-C_6)$(alkyl) and $-N((C_1-C_6)(alkyl))_2$.

2. The compound according to claim 1, wherein T is selected from the group consisting of:

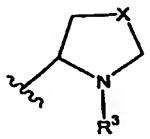


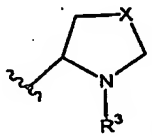
3. The compound according to claim 2,

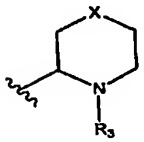
wherein X is independently selected from the group consisting of O, S, NR^{22}, and $(CR^{22}R^{23})$;

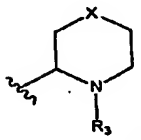
R^{22} and R^{23} are independently selected from H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, $-(C=O)-R^4$, $(CR^4R^5)_t(C_3-C_{12})$cycloalkyl, $(CR^4R^5)_t(C_6-C_{12})$aryl, and $(CR^4R^5)_t$(4-10)-membered heterocyclyl;

wherein each carbon atom of $R^{22}$and R^{23} is optionally substituted by 1 or more R^6 groups.

4. The compound according to claim 3, wherein T is  and wherein X is O.

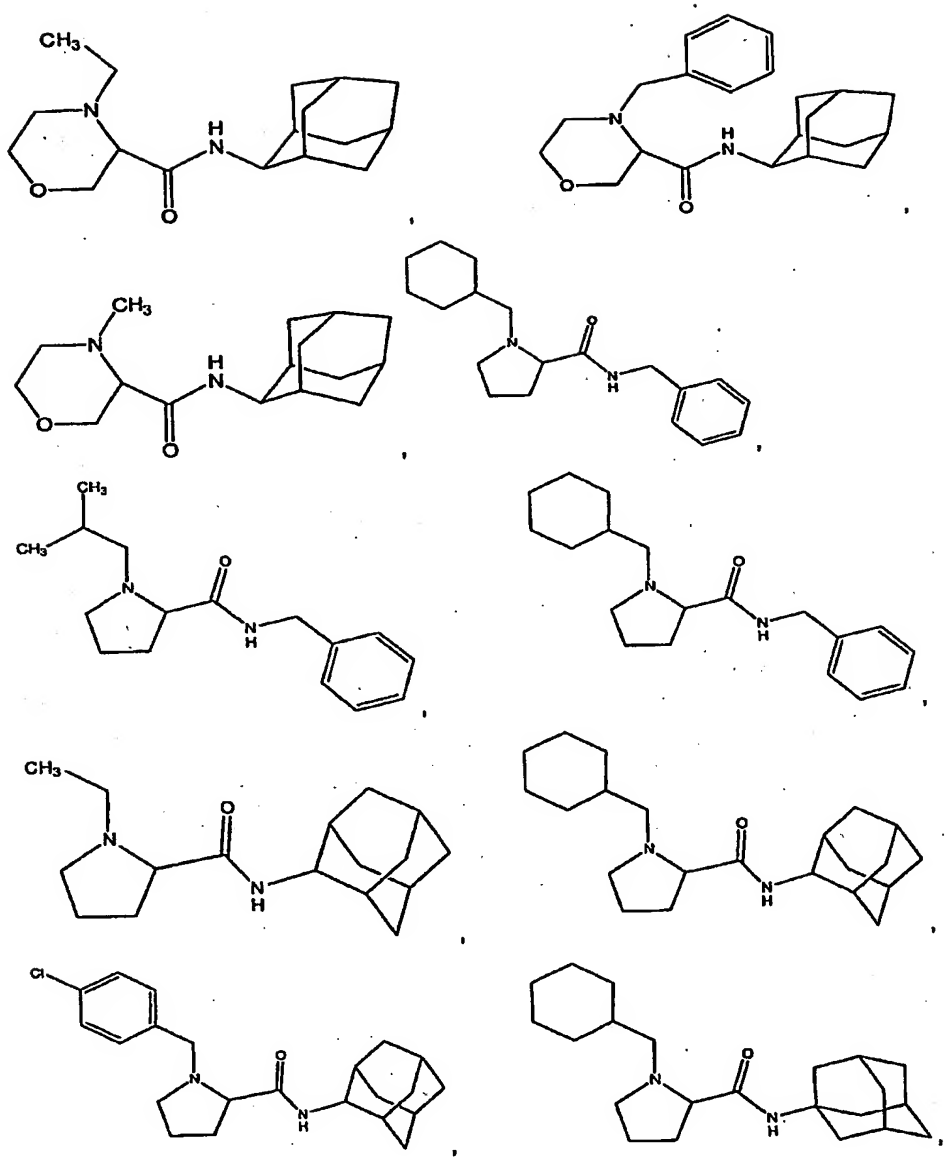
5. The compound according to claim 3, wherein T is  and wherein X is $CR^{22}R^{23}$.

6. The compound according to claim 3, wherein T is  and wherein X is O.

7. The compound according to claim 3, wherein T is  and wherein X is $CR^{22}R^{23}$.

8. The compound according to claim 1 wherein R^1 is adamantyl, benzyl, phenyl, picolyl, isoindolinyl, pyridinyl, isoquinolyl, or cyclohexyl, wherein each carbon atom is optionally substituted by 1 to 10 R^6 groups; wherein each R^6 is independently selected from the group consisting of halo, cyano, CF_3, hydroxy, $(C_1$-$C_6)$alkoxy, $(C_1$–$C_6)$alkyl, and $(C_2$-$C_6)$alkenyl.

9. A compound selected from the group consisting of:



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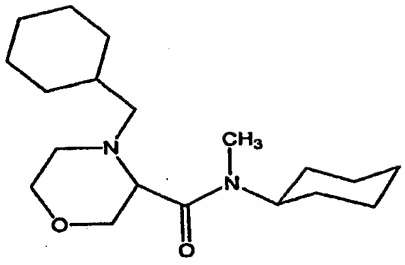
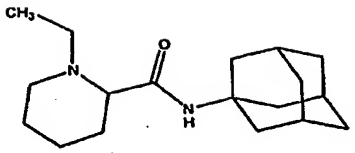
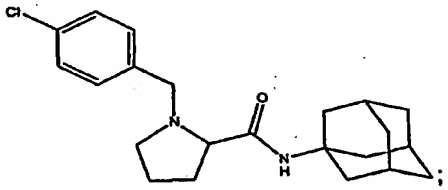
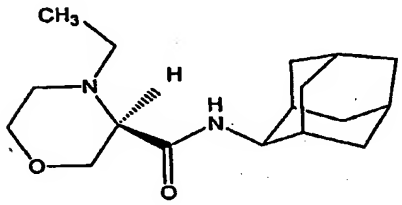
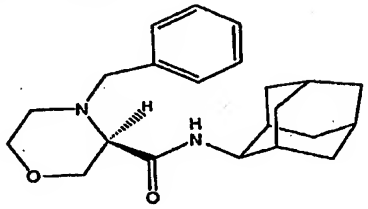


and


;

or a pharmaceutically acceptable salt or solvate thereof.

10. A compound selected from the group consisting of:

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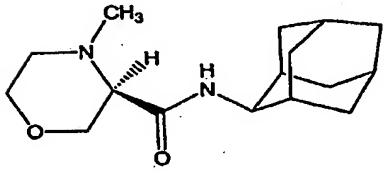
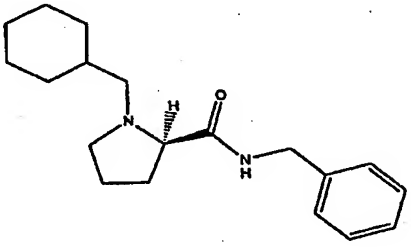
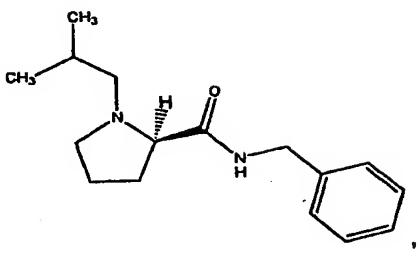
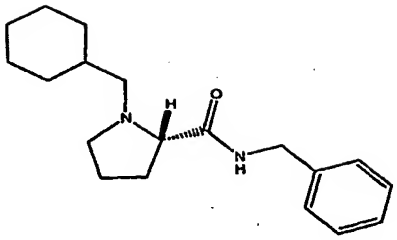
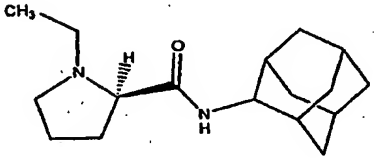
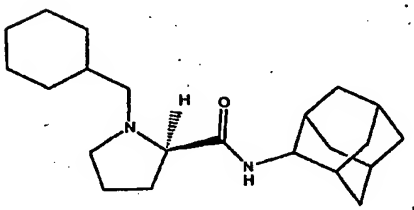
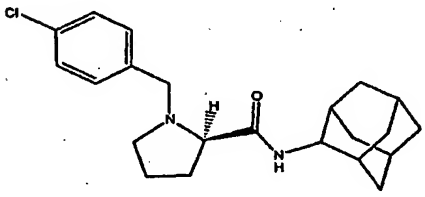



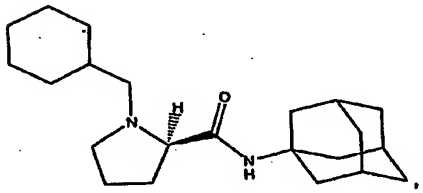


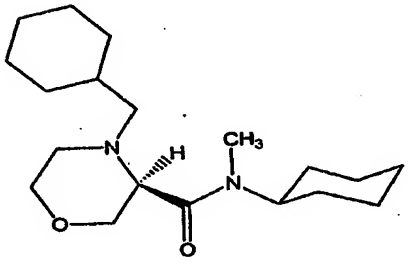


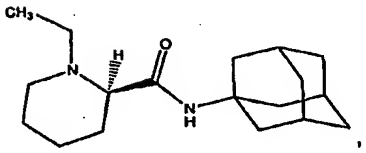




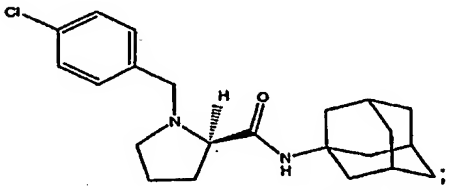








and



or a pharmaceutically acceptable salt or solvate thereof.

11. A pharmaceutical composition comprising an effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

12. A method of treating a condition that is mediated by the modulation of the 11-β-hsd-1 enzyme, the method comprising administering to a mammal an effective amount of a compound, according to claim 1, or a pharmaceutically acceptable salt or solvate thereof.

13. A method of treating diabetes, metabolic syndrome, insulin resistance syndrome, obesity, glaucoma, hyperlipidemia, hyperglycemia, hyperinsulinemia, osteoporosis, tuberculosis, atherosclerosis, dementia, depression, viral diseases, ophthalmic disorders, inflammatory disorders, or diseases in which the liver is a target organ, the method comprising administering to a mammal an effective amount of a compound, according to claim 1, or a pharmaceutically acceptable salt or solvate thereof.

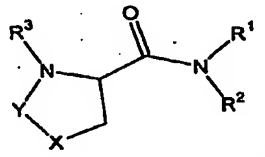
14. A method of treating a condition that is mediated by the modulation of the 11-β-hsd-1 enzyme, the method comprising administering to a mammal an effective amount of a compound, according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, with a known therapeutic agent to treat glaucoma.

15. The method of treating a condition, according to claim 12, comprising administering to a mammal an effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, with a prostanoid receptor agonist such as latanoprost to treat glaucoma.

16. The method of treating a condition, according to claim 12, comprising administering to a mammal an effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, with a known therapeutic agent such as carbonic anhydrase inhibitor to treat glaucoma.

17. The method of treating a condition, according to claim 12, comprising administering to a mammal an effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, with a known therapeutic agent such as PPAR agonists to treat diabetes.

18. A method of preparing a compound of formula (V)



(V);

wherein R^1 is selected from the group consisting of $(C_1\text{-}C_6)$alkyl; $(CR^4R^5)_t(C_3\text{-}C_{12})$cycloalkyl, $(CR^4R^5)_t(C_6\text{-}C_{12})$aryl, and $(CR^4R^5)_t$(4-10)-membered heterocyclyl;

R^2 is selected from the group consisting of H and $(C_1\text{-}C_6)$alkyl;

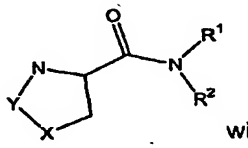
R^3 is selected from the group consisting of $(C_1\text{-}C_6)$alkyl and $NR^{22}R^{23}$;

R^4 and R^5 are independently selected from H and $(C_1\text{-}C_6)$alkyl;

R^{22} and R^{23} are independently selected from H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $-(C{=}O)\text{-}R^4$, $(CR^4R^5)_t(C_3\text{-}C_{12})$cycloalkyl, $(CR^4R^5)_t(C_6\text{-}C_{12})$aryl, and $(CR^4R^5)_t$(4-10)-membered heterocyclyl;

X is independently selected from the group consisting of $CR^{22}R^{23}$, O, S, and NR^{22};

Y is $(CR^{22}R^{23})_n$ wherein n is independently selected from 1, 2, and 3; comprising:

treating a compound of formula (IV)  with R^3-LV in a solvent;

wherein LV is a suitable leaving group and R^3 is defined above.

19. A method according to claim 18, further comprising treating a compound of formula (IV) to form a compound of formula (V) in the presence of a base.

20. A method according to claim 19, further comprising the base selected from the group consisting of K_2CO_3, $NaHCO_3$, and Et_3N.

21. A method according to claim 18, further comprising treating a compound of formula (IV) to form a compound of formula (V) at a temperature range from about 20 degrees Celsius to the boiling point of the solvent.

22. A method according to claim 18, further comprising treating a compound of formula (IV) to form a compound of formula (V) by reductive amination in the presence of an aldehyde or ketone in a suitable solvent.

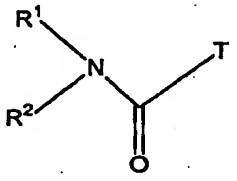
35. A method according to claim 34, wherein the amine is selected from the group consisting of 2-adamantanamine-hydrochloride salt and benzyl amine.

36. A method according to claim 34, further comprising the step of preparing the compound of formula (III) from a compound of formula (II) by treating the compound of formula (II) with at least one activating agent.

37. A method according to claim 36, wherein the at least one activating agent is selected from the group consisting of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, 1-hydroxybenzotriazole, and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

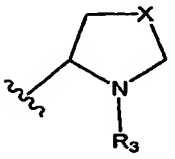
Abstract of the Invention

The present invention relates to compounds with the formula (I), or a pharmaceutically acceptable salt thereof:

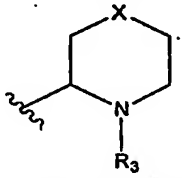


(I);

wherein T is a (4-10)-membered heterocyclyl selected from the group consisting of



and



and wherein R^1, R^2 and R^3 are as defined in the specification. The invention also relates to pharmaceutical compositions comprising the compounds of formula (I) and methods of treating a condition that is mediated by the modulation of the 11-β-hsd-1 enzyme, the method comprising administering to a mammal an effective amount of a compound of formula (I).